COLLECTIVE VARIABLES MODULE
Reference manual for LAMMPS

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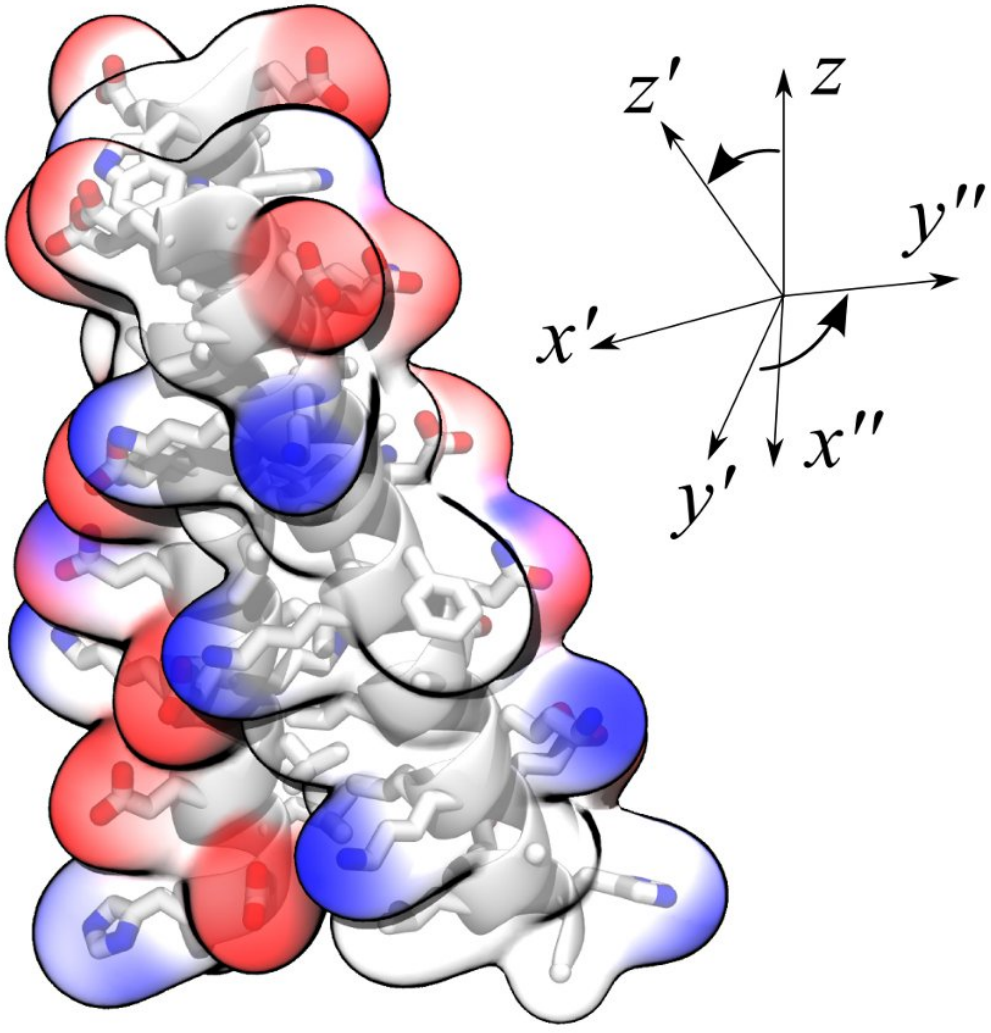

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1 Introduction

In today's molecular dynamics simulations, it is often useful to reduce the large number of degrees of freedom of a physical system into few parameters whose statistical distributions can be analyzed individually, or used to define biasing potentials to alter the dynamics of the system in a controlled manner. These have been called 'order parameters', 'collective variables', '(surrogate) reaction coordinates', and many other terms.

Here we use primarily the term 'collective variable' (shortened to *colvar*), which indicates any differentiable function of atomic Cartesian coordinates, x_i, with i between 1 and N, the total number of atoms:

$$\xi(t) = \xi\left(x_i(t), x_j(t), x_k(t), \ldots\right) \ , \ \ 1 \leq i, j, k \ldots \leq N \tag{1}$$

This manual documents the collective variables module (**Colvars**), a portable software that interfaces multiple MD simulation programs, with a focus on flexibility, robustness and high performance. The module is designed to perform multiple tasks concurrently during or after a simulation, the most common of which are:

- apply restraints or biasing potentials to multiple colvars, tailored on the system by choosing from a wide set of basis functions, without limitations on their number or on the number of atoms involved;
- calculate potentials of mean force (PMFs) along any set of colvars, using different enhanced sampling methods, such as Adaptive Biasing Force (ABF), metadynamics, steered MD and umbrella sampling; variants of these methods that make use of an ensemble of replicas are supported as well;
- calculate statistical properties of the colvars, such as running averages and standard deviations, correlation functions of pairs of colvars, and multidimensional histograms: this can be done either at run-time without the need to save very large trajectory files, or after a simulation has been completed using VMD and the `cv` command.

To briefly illustrate the flexibility of the Colvars module, Figure 1 shows an example of a non-trivial configuration (the corresponding input can be found in 2.2).

Detailed explanations of the design of the Colvars module are provided in reference [1]. Please cite this reference whenever publishing work that makes use of this module.

2 General parameters and input/output files

Here, we document the syntax of the commands and parameters used to set up and use the Colvars module in LAMMPS. One of these parameters is the configuration file or the configuration text for the module itself, whose syntax is described in 2.2 and in the following sections.

2.1 LAMMPS keywords

To enable a Colvars-based calculation, the following line must be added to the LAMMPS configuration file:

`fix` *ID* `all colvars` *configfile keyword value pairs ...*

where *ID* is a string that uniquely identifies this fix command inside a LAMMPS script, *configfile* is the name of the configuration file for the Colvars module, followed by one or more of the following optional keywords with their corresponding arguments:

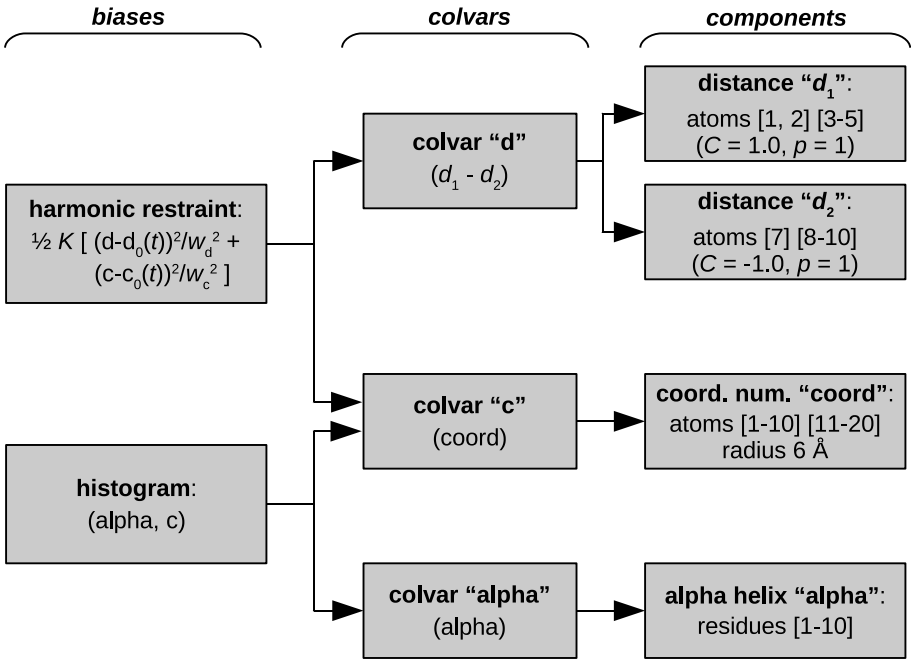

Figure 1: Graphical representation of a Colvars configuration (**note:** *currently, the α-helical content colvar is unavailable in LAMMPS)*. The colvar called "*d*" is defined as the difference between two distances: the first distance (d_1) is taken between the center of mass of atoms 1 and 2 and that of atoms 3 to 5, the second (d_2) between atom 7 and the center of mass of atoms 8 to 10. The difference $d = d_1 - d_2$ is obtained by multiplying the two by a coefficient $C = +1$ or $C = -1$, respectively. The colvar called "*c*" is the coordination number calculated between atoms 1 to 10 and atoms 11 to 20. A harmonic restraint is applied to both d and c: to allow using the same force constant K, both d and c are scaled by their respective fluctuation widths w_d and w_c. The values of "*c*" are also recorded throughout the simulation as a joint 2-dimensional histogram.

- `input` ⟨Name or prefix of the input state file⟩
  Context: Keyword of the `fix colvars` command
  Acceptable values: string
  Description: If a value is provided, it is interpreted as either the name of the input state file, or as the prefix of the file named *input*`.colvars.state`. This allows to continue a previous collective variables-based calculation when a regular binary LAMMPS restart file is not available (see 2.3).

- `output` ⟨Prefix of the output state file⟩
  Context: Keyword of the `fix colvars` command
  Acceptable values: string
  Default value: "out"
  Description: If a value is provided, it is interpreted as the prefix to all output files that will be written by the Colvars module (see 2.4).

- `unwrap` ⟨Whether to unwrap coordinates passed to the Colvars module⟩
  Context: keyword of the `fix colvars` command
  Acceptable values: "yes" or "no"
  Default value: "yes"
  Description: This keyword controls whether wrapped or unwrapped coordinates are passed to the

Colvars module for calculation of the collective variables and of the resulting forces. The default is to use the image flags to reconstruct the absolute atom positions: under this convention, centers of mass and centers of geometry are calculated as a weighted vector sum (see 4.3). Setting this to *no* will use the current local coordinates that are wrapped back into the simulation cell at each re-neighboring instead.

- `seed` ⟨Seed for the random number generator⟩
  Context: Keyword of the `fix colvars` command
  Acceptable values: positive integer
  Default value: 1966
  Description: If defined, the value of this keyword is provided as seed to the random number generator. This is only meaningful when the `extendedLangevinDamping` keyword is used (see 3.3).

- `tstat` ⟨Thermostating fix⟩
  Context: Keyword of the `fix colvars` command
  Acceptable values: string
  Default value: NULL
  Description: This keyword provides the *ID* of an applicable thermostating fix command. This will be used to provide the Colvars module with the current thermostat target temperature when using a method that needs this information.

2.2 Configuration syntax for the Colvars module

The syntax of the Colvars configuration is "`keyword value`", where the keyword and its value are separated by any white space. The following rules apply:

- keywords are case-insensitive (`upperBoundary` is the same as `upperboundary` and `UPPERBOUNDARY`): their string values are however case-sensitive (e.g. file names);
- a long value or a list of multiple values can be distributed across multiple lines by using curly braces, "{" and "}": the opening brace "{" must occur on the same line as the keyword, following a space character or other white space; the closing brace "}" can be at any position after that;
- many keywords are nested, and are only meaningful within a specific context: for every keyword documented in the following, the "parent" keyword that defines such context is also indicated;
- if a keyword requiring a boolean value (`yes|on|true` or `no|off|false`) is provided without an explicit value, it defaults to '`yes|on|true`'; for example, '`outputAppliedForce`' may be used as shorthand for '`outputAppliedForce on`';
- the hash character # indicates a comment: all text in the same line following this character will be ignored.

The following keywords are available in the global context of the colvars configuration, i.e. they are not nested inside other keywords:

- `colvarsTrajFrequency` ⟨Colvar value trajectory frequency⟩
  Context: global
  Acceptable values: positive integer
  Default value: `100`
  Description: The values of each colvar (and of other related quantities, if requested) are written to

the file *output*`.colvars.traj` every these many steps throughout the simulation. If the value is `0`, such trajectory file is not written. For optimization the output is buffered, and synchronized with the disk only when the restart file is being written.

- `colvarsTrajAppend` ⟨Append to trajectory file?⟩
  Context: global
  Acceptable values: boolean
  Default value: `off`
  Description: If this flag is enabled, and a file with the same name as the trajectory file is already present, new data is appended to that file. Otherwise, a new file is created with the same name that overwrites the previous file.

- `colvarsRestartFrequency` ⟨Colvar module restart frequency⟩
  Context: global
  Acceptable values: positive integer
  Default value: `restartFreq`
  Description: Allows to choose a different restart frequency for the Colvars module. Redefining it may be useful to trace the time evolution of those few properties which are not written to the trajectory file for reasons of disk space.

- `indexFile` ⟨Index file for atom selection (GROMACS "ndx" format)⟩
  Context: global
  Acceptable values: UNIX filename
  Description: This option reads an index file (usually with a `.ndx` extension) as produced by the `make_ndx` tool of GROMACS. This keyword may be repeated to load multiple index files: the same group name cannot appear in multiple index files. In LAMMPS, the `group2ndx` command can be used to generate such file from existing groups. Note that the Colvars module reads the indices of atoms from the index file: therefore, the LAMMPS groups do not need to remain active during the simulation, and could be deleted right after issuing `group2ndx`. The names of index groups contained in this file can then be used to define atom groups with the `indexGroup` keyword. Other supported methods to select atoms are described in 4.

- `smp` ⟨Whether SMP parallelism should be used⟩
  Context: global
  Acceptable values: boolean
  Default value: `on`
  Description: If this flag is enabled (default), SMP parallelism over threads will be used to compute variables and biases, provided that this is supported by LAMMPS.

- `analysis` ⟨Turn on run-time statistical analysis⟩
  Context: global
  Acceptable values: boolean
  Default value: `off`
  Description: If this flag is enabled, each colvar is instructed to perform whatever run-time statistical analysis it is configured to, such as correlation functions, or running averages and standard deviations. See section 3.4 for details.

The example below defines the same configuration shown in Fig. 1. The options within the `colvar` blocks are described in 3 and 5, the ones within the `harmonic` and `histogram` blocks in 6. **Note:** *except*

`colvar`, *none of the keywords shown is mandatory*.

```
colvar {
  # difference of two distances
  name d
  width 0.2 # 0.2 Å of estimated fluctuation width
  distance {
    componentCoeff 1.0
    group1 { atomNumbers 1 2 }
    group2 { atomNumbers 3 4 5 }
  }
  distance {
    componentCoeff -1.0
    group1 { atomNumbers 7 }
    group2 { atomNumbers 8 9 10 }
  }
}

colvar {
  name c
  coordNum {
    cutoff 6.0
    group1 { atomNumbersRange 1-10 }
    group2 { atomNumbersRange 11-20 }
  }
}


harmonic {
  colvars d c
  centers 3.0 4.0
  forceConstant 5.0
}

histogram {
  colvars c
}
```

Section 3 explains how to define a colvar and its behavior, regardless of its specific functional form. To define colvars that are appropriate to a specific physical system, Section 4 documents how to select atoms, and section 5 lists all of the available functional forms, which we call "colvar components". Finally, section 6 lists the available methods and algorithms to perform biased simulations and multidimensional analysis of colvars.

2.3 Input state file (optional)

Aside from the colvars configuration, an optional input state file may be provided to load the relevant data from a previous simulation. The name of this file is provided as the argument to the `input` keyword of the

`fix ID all colvars` command. The same information is stored in the binary restart files of LAMMPS, so it not needed when continuing a calculation from such a restart.

2.4 Output files

During a simulation with collective variables defined, the following three output files are written:

- a *state file*, named *output*`.colvars.state`; this file is in ASCII format;
- if the parameter `colvarsRestartFrequency` is larger than zero, a *restart file* named *restart*`.colvars.state` is written every that many steps: this file is equivalent to the final state file;
- if the parameter `colvarsTrajFrequency` is greater than 0 (default: 100), a *trajectory file* is written during the simulation: its name is *output*`.colvars.traj`; unlike the state file, it is not needed to restart a simulation, but can be used later for post-processing and analysis.

Other output files may be written by specific methods applied to the colvars (e.g. by the ABF method, see 6.1, or the metadynamics method, see 6.3). Like the colvar trajectory file, they are needed only for analyzing, not continuing a simulation. All such files' names also begin with the prefix *output*.

3 Defining collective variables and their properties

In the configuration file each colvar is defined by the keyword `colvar`, followed by its configuration options within curly braces: `colvar { ... }`. One of these options is the name of a colvar component: for example, including `rmsd { ... }` defines the colvar as a RMSD function. *In most applications, only one component is used, and the component is equal to the colvar.*

The full list of colvar components can be found in Section 5, with the syntax to select atoms in Section 4. The following section lists several options to control the behavior of a single colvar, regardless of its type.

3.1 General options for a collective variable

The following options are not required by default; however, the first four are very frequently used:

- `name` ⟨Name of this colvar⟩
  Context: `colvar`
  Acceptable values: string
  Default value: "`colvar`" + numeric id
  Description: The name is an unique case-sensitive string which allows the Colvars module to identify this colvar unambiguously; it is also used in the trajectory file to label to the columns corresponding to this colvar.

- `width` ⟨Colvar fluctuation scale, or resolution for grid-based methods⟩
  Context: `colvar`
  Acceptable values: positive decimal
  Default value: 1.0
  Description: This number has the same physical unit as the colvar value and defines an effective colvar unit. Biasing algorithms use it for different purposes. Harmonic restraints (6.4) use it to set the physical unit of the force constant, which is useful for multidimensional restraints involving colvars with different units or scale which may then be defined by a single, scaled force constant. Histogram (6.8) and ABF biases (6.1) interpret it as the grid spacing in the direction of this variable.

Metadynamics (6.3) uses it to set the width of newly added hills. In other cases, it is simplest to keep the default value of 1, so that harmonic force constants are provided in their usual physical unit. When a non-unity width is required by the application, the optimal value is application-dependent, but can often be thought of as a user-provided estimate of the fluctuation amplitude for the colvar. In those cases, it should generally be set smaller than or equal to the standard deviation of the colvar during a very short simulation run.

- `lowerBoundary` ⟨Lower boundary of the colvar⟩
  Context: `colvar`
  Acceptable values: decimal
  Description: Defines the lowest end of the interval of "relevant" values for the colvar. This number can be either a true physical boundary, or a user-defined number. Together with `upperBoundary` and `width`, it is used to define a grid of values along the colvar (not available for colvars based on `distanceDir`, `distanceVec`, and `orientation`). This option does not affect dynamics: to confine a colvar within a certain interval, the options `lowerWall` and `lowerWallConstant` should be used.

- `upperBoundary` ⟨Upper boundary of the colvar⟩
  Context: `colvar`
  Acceptable values: decimal
  Description: Similarly to `lowerBoundary`, defines the highest possible or allowed value.

- `hardLowerBoundary` ⟨Whether the lower boundary is the physical lower limit⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `off`
  Description: This option does not affect simulation results, but enables some internal optimizations. Depending on its mathematical definition, a colvar may have "natural" boundaries: for example, a `distance` colvar has a "natural" lower boundary at 0. Setting this option instructs the Colvars module that the user-defined lower boundary is "natural". See Section 5 for the physical ranges of values of each component.

- `hardUpperBoundary` ⟨Whether the upper boundary is the physical upper limit of the colvar's values⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `off`
  Description: Analogous to `hardLowerBoundary`.

- `expandBoundaries` ⟨Allow to expand the two boundaries if needed⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `off`
  Description: If defined, biasing and analysis methods may keep their own copies of `lowerBoundary` and `upperBoundary`, and expand them to accommodate values that do not fit in the initial range. Currently, this option is used by the metadynamics bias (6.3) to keep all of its hills fully within the grid. This option cannot be used when the initial boundaries already span the full period of a periodic colvar.

- `subtractAppliedForce` ⟨Do not include biasing forces in the total force for this colvar⟩
  Context: `colvar`

Acceptable values: boolean
Default value: `off`
Description: If the colvar supports total force calculation (see 5.3.3), all forces applied to this colvar by biases will be removed from the total force. This keyword allows to recover some of the "system force" calculation available in the Colvars module before version 2016-08-10. Please note that removal of *all* other external forces (including biasing forces applied to a different colvar) is *no longer supported*, due to changes in the underlying simulation engines (primarily NAMD). This option may be useful when continuing a previous simulation where the removal of external/applied forces is essential. *For all new simulations, the use of this option is not recommended.*

3.2 Trajectory output

- `outputValue` ⟨Output a trajectory for this colvar⟩
Context: `colvar`
Acceptable values: boolean
Default value: `on`
Description: If `colvarsTrajFrequency` is non-zero, the value of this colvar is written to the trajectory file every `colvarsTrajFrequency` steps in the column labeled "<name>".

- `outputVelocity` ⟨Output a velocity trajectory for this colvar⟩
Context: `colvar`
Acceptable values: boolean
Default value: `off`
Description: If `colvarsTrajFrequency` is defined, the finite-difference calculated velocity of this colvar are written to the trajectory file under the label "v_<name>".

- `outputEnergy` ⟨Output an energy trajectory for this colvar⟩
Context: `colvar`
Acceptable values: boolean
Default value: `off`
Description: This option applies only to extended Lagrangian colvars. If `colvarsTrajFrequency` is defined, the kinetic energy of the extended degree and freedom and the potential energy of the restraining spring are are written to the trajectory file under the labels "Ek_<name>" and "Ep_<name>".

- `outputTotalForce` ⟨Output a total force trajectory for this colvar⟩
Context: `colvar`
Acceptable values: boolean
Default value: `off`
Description: If `colvarsTrajFrequency` is defined, the total force on this colvar (i.e. the projection of all atomic total forces onto this colvar — see equation (15) in section 6.1) are written to the trajectory file under the label "fs_<name>". For extended Lagrangian colvars, the "total force" felt by the extended degree of freedom is simply the force from the harmonic spring. **Note:** not all components support this option. The physical unit for this force is the unit of energy specified by `units`, divided by the colvar unit U.

- `outputAppliedForce` ⟨Output an applied force trajectory for this colvar⟩
Context: `colvar`
Acceptable values: boolean
Default value: `off`

Description: If `colvarsTrajFrequency` is defined, the total force applied on this colvar by Colvars biases are written to the trajectory under the label "`fa_<name>`". For extended Lagrangian colvars, this force is actually applied to the extended degree of freedom rather than the geometric colvar itself. The physical unit for this force is the unit of energy specified by `units` divided by the colvar unit.

3.3 Extended Lagrangian.

The following options enable extended-system dynamics, where a colvar is coupled to an additional degree of freedom (fictitious particle) by a harmonic spring. All biasing and confining forces are then applied to the extended degree of freedom. The "actual" geometric colvar (function of Cartesian coordinates) only feels the force from the harmonic spring. This is particularly useful when combined with an ABF bias (6.1) to perform eABF simulations (6.2).

- `extendedLagrangian` ⟨Add extended degree of freedom⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `off`
  Description: Adds a fictitious particle to be coupled to the colvar by a harmonic spring. The fictitious mass and the force constant of the coupling potential are derived from the parameters `extendedTimeConstant` and `extendedFluctuation`, described below. Biasing forces on the colvar are applied to this fictitious particle, rather than to the atoms directly. This implements the extended Lagrangian formalism used in some metadynamics simulations [2].

- `extendedFluctuation` ⟨Standard deviation between the colvar and the fictitious particle (colvar unit)⟩
  Context: `colvar`
  Acceptable values: positive decimal
  Description: Defines the spring stiffness for the `extendedLagrangian` mode, by setting the typical deviation between the colvar and the extended degree of freedom due to thermal fluctuation. The spring force constant is calculated internally as $k_B T/\sigma^2$, where σ is the value of `extendedFluctuation`.

- `extendedTimeConstant` ⟨Oscillation period of the fictitious particle (fs)⟩
  Context: `colvar`
  Acceptable values: positive decimal
  Default value: `200`
  Description: Defines the inertial mass of the fictitious particle, by setting the oscillation period of the harmonic oscillator formed by the fictitious particle and the spring. The period should be much larger than the MD time step to ensure accurate integration of the extended particle's equation of motion. The fictitious mass is calculated internally as $k_B T(\tau/2\pi\sigma)^2$, where τ is the period and σ is the typical fluctuation (see above).

- `extendedTemp` ⟨Temperature for the extended degree of freedom (K)⟩
  Context: `colvar`
  Acceptable values: positive decimal
  Default value: thermostat temperature
  Description: Temperature used for calculating the coupling force constant of the extended variable (see `extendedFluctuation`) and, if needed, as a target temperature for extended Langevin dynamics (see `extendedLangevinDamping`). This should normally be left at its default value.

- `extendedLangevinDamping` ⟨Damping factor for extended Langevin dynamics (ps^{-1})⟩
  Context: `colvar`
  Acceptable values: positive decimal
  Default value: `1.0`
  Description: If this is non-zero, the extended degree of freedom undergoes Langevin dynamics at temperature `extendedTemp`. The friction force is minus `extendedLangevinDamping` times the velocity. This is useful because the extended dynamics coordinate may heat up in the transient non-equilibrium regime of ABF. Use moderate damping values, to limit viscous friction (potentially slowing down diffusive sampling) and stochastic noise (increasing the variance of statistical measurements). In doubt, use the default value.

3.4 Statistical analysis of collective variables

When the global keyword `analysis` is defined in the configuration file, run-time calculations of statistical properties for individual colvars can be performed. At the moment, several types of time correlation functions, running averages and running standard deviations are available.

- `corrFunc` ⟨Calculate a time correlation function?⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `off`
  Description: Whether or not a time correlaction function should be calculated for this colvar.

- `corrFuncWithColvar` ⟨Colvar name for the correlation function⟩
  Context: `colvar`
  Acceptable values: string
  Description: By default, the auto-correlation function (ACF) of this colvar, ξ_i, is calculated. When this option is specified, the correlation function is calculated instead with another colvar, ξ_j, which must be of the same type (scalar, vector, or quaternion) as ξ_i.

- `corrFuncType` ⟨Type of the correlation function⟩
  Context: `colvar`
  Acceptable values: `velocity`, `coordinate` or `coordinate_p2`
  Default value: `velocity`
  Description: With `coordinate` or `velocity`, the correlation function $C_{i,j}(t) = \left\langle \Pi\left(\xi_i(t_0), \xi_j(t_0+t)\right)\right\rangle$ is calculated between the variables ξ_i and ξ_j, or their velocities. $\Pi(\xi_i, \xi_j)$ is the scalar product when calculated between scalar or vector values, whereas for quaternions it is the cosine between the two corresponding rotation axes. With `coordinate_p2`, the second order Legendre polynomial, $(3\cos(\theta)^2 - 1)/2$, is used instead of the cosine.

- `corrFuncNormalize` ⟨Normalize the time correlation function?⟩
  Context: `colvar`
  Acceptable values: boolean
  Default value: `on`
  Description: If enabled, the value of the correlation function at $t = 0$ is normalized to 1; otherwise, it equals to $\left\langle O(\xi_i, \xi_j)\right\rangle$.

- `corrFuncLength` ⟨Length of the time correlation function⟩
  Context: `colvar`
  Acceptable values: positive integer

Default value: 1000
Description: Length (in number of points) of the time correlation function.

- corrFuncStride ⟨Stride of the time correlation function⟩
  Context: colvar
  Acceptable values: positive integer
  Default value: 1
  Description: Number of steps between two values of the time correlation function.

- corrFuncOffset ⟨Offset of the time correlation function⟩
  Context: colvar
  Acceptable values: positive integer
  Default value: 0
  Description: The starting time (in number of steps) of the time correlation function (default: $t = 0$).
  Note: *the value at t = 0 is always used for the normalization.*

- corrFuncOutputFile ⟨Output file for the time correlation function⟩
  Context: colvar
  Acceptable values: UNIX filename
  Default value: <name>.corrfunc.dat
  Description: The time correlation function is saved in this file.

- runAve ⟨Calculate the running average and standard deviation⟩
  Context: colvar
  Acceptable values: boolean
  Default value: off
  Description: Whether or not the running average and standard deviation should be calculated for this colvar.

- runAveLength ⟨Length of the running average window⟩
  Context: colvar
  Acceptable values: positive integer
  Default value: 1000
  Description: Length (in number of points) of the running average window.

- runAveStride ⟨Stride of the running average window values⟩
  Context: colvar
  Acceptable values: positive integer
  Default value: 1
  Description: Number of steps between two values within the running average window.

- runAveOutputFile ⟨Output file for the running average and standard deviation⟩
  Context: colvar
  Acceptable values: UNIX filename
  Default value: <name>.runave.dat
  Description: The running average and standard deviation are saved in this file.

4 Selecting atoms for colvars: defining atom groups

4.1 Selection keywords

To define collective variables, atoms are usually selected by group. Each group is identified by a name that is unique in the context of the specific colvar component (e.g. for a distance component, the names of the two groups are `group1` and `group2`). The name is followed by a brace-delimited block of selection keywords: these may be used individually or in combination with each other, and each can be repeated any number of times. Selection is incremental: each keyword adds the corresponding atoms to the selection, so that different sets of atoms can be combined. However, atoms included by multiple keywords are only counted once. Below is an example configuration for an atom group named "`atoms`", which uses an unusually varied combination of selection keywords:

```
atoms {

  # add atoms 1 and 3 to this group (note: the first atom in the system is 1)
  atomNumbers {
    1 3
  }

  # add atoms starting from 20 up to and including 50
  atomNumbersRange 20-50

  # add index group (requires a .ndx file to be provided globally)
  indexGroup Water
}
```

The resulting selection includes atoms 1 and 3, those between 20 and 50, and those in the index group called "Water"; the indices of this group are read from the file provided by `indexFile`, in the global section of the configuration file.

The complete list of selection keywords available in LAMMPS is:

- `atomNumbers` ⟨List of atom numbers⟩
  Context: atom group
  Acceptable values: space-separated list of positive integers
  Description: This option adds to the group all the atoms whose numbers are in the list. *The number of the first atom in the system is 1: to convert from a VMD selection, use "atomselect get serial".*

- `indexGroup` ⟨Name of index group to be used (GROMACS format)⟩
  Context: atom group
  Acceptable values: string
  Description: If the name of an index file has been provided by `indexFile`, this option allows to select one index group from that file: the atoms from that index group will be used to define the current group.

- `atomNumbersRange` ⟨Atoms within a number range⟩
  Context: atom group
  Acceptable values: <Starting number>-<Ending number>
  Description: This option includes in the group all atoms whose numbers are within the range specified. *The number of the first atom in the system is 1.*

- `dummyAtom` ⟨Dummy atom position (Å)⟩
  Context: atom group
  Acceptable values: `(x, y, z)` triplet
  Description: Instead of selecting any atom, this option makes the group a virtual particle at a fixed position in space. This is useful e.g. to replace a group's center of geometry with a user-defined position.

4.2 Moving frame of reference.

The following options define an automatic calculation of an optimal translation (`centerReference`) or optimal rotation (`rotateReference`), that superimposes the positions of this group to a provided set of reference coordinates. This can allow, for example, to effectively remove from certain colvars the effects of molecular tumbling and of diffusion. Given the set of atomic positions $\mathbf{x}_i$, the colvar ξ can be defined on a set of roto-translated positions $\mathbf{x}'_i = R(\mathbf{x}_i - \mathbf{x}^{\mathrm{C}}) + \mathbf{x}^{\mathrm{ref}}$. $\mathbf{x}^{\mathrm{C}}$ is the geometric center of the $\mathbf{x}_i$, R is the optimal rotation matrix to the reference positions and $\mathbf{x}^{\mathrm{ref}}$ is the geometric center of the reference positions.

Components that are defined based on pairwise distances are naturally invariant under global roto-translations. Other components are instead affected by global rotations or translations: however, they can be made invariant if they are expressed in the frame of reference of a chosen group of atoms, using the `centerReference` and `rotateReference` options. Finally, a few components are defined by convention using a roto-translated frame (e.g. the minimal RMSD): for these components, `centerReference` and `rotateReference` are enabled by default. In typical applications, the default settings result in the expected behavior.

- `centerReference` ⟨Implicitly remove translations for this group⟩
  Context: atom group
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is `on`, the center of geometry of the group will be aligned with that of the reference positions provided by `refPositions` or `refPositionsFile`. Colvar components will only have access to the aligned positions. **Note**: unless otherwise specified, `rmsd` and `eigenvector` set this option to `on` *by default*.

- `rotateReference` ⟨Implicitly remove rotations for this group⟩
  Context: atom group
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is `on`, the coordinates of this group will be optimally superimposed to the reference positions provided by `refPositions` or `refPositionsFile`. The rotation will be performed around the center of geometry if `centerReference` is `on`, around the origin otherwise. The algorithm used is the same employed by the `orientation` colvar component [3]. Forces applied to the atoms of this group will also be implicitly rotated back to the original frame. **Note**: unless otherwise specified, `rmsd` and `eigenvector` set this option to `on` *by default*.

- `refPositions` ⟨Reference positions for fitting (Å)⟩
  Context: atom group
  Acceptable values: space-separated list of `(x, y, z)` triplets
  Description: This option provides a list of reference coordinates for `centerReference` or `rotateReference`. If only `centerReference` is `on`, the list may contain a single (x, y, z) triplet; if also `rotateReference` is `on`, the list should be as long as the atom group.

- `refPositionsFile` ⟨File containing the reference positions for fitting⟩
  Context: atom group
  Acceptable values: UNIX filename
  Description: This keyword provides the reference coordinates for fitting from the given file, and is mutually exclusive with `refPositions`. The acceptable file format is XYZ. Atomic positions are read differently depending on the three following scenarios: *i)* the file contains exactly as many records as the atoms in the group: all positions are read in sequence; *ii)* the file contains coordinates for the entire system: only the positions corresponding to the numeric indices of the atom group are read.

- `fittingGroup` ⟨Use an alternate set of atoms to define the roto-translation⟩
  Context: atom group
  Acceptable values: Block `fittingGroup { ... }`
  Default value: This group itself
  Description: If either `centerReference` or `rotateReference` is defined, this keyword defines an alternate atom group to calculate the optimal roto-translation. Use this option to define a continuous rotation if the structure of the group involved changes significantly (a typical symptom would be the message "Warning: discontinuous rotation!").

```
# Example: defining a group "atoms", with its coordinates expressed
# on a roto-translated frame of reference defined by a second group
atoms {

  psfSegID PROT
  atomNameResidueRange CA 41-48

  centerReference yes
  rotateReference yes
  fittingGroup {
    # define the frame by fitting the rest of the protein
    psfSegID PROT PROT
    atomNameResidueRange CA 1-40
    atomNameResidueRange CA 49-100
  }
  refPositionsFile all.pdb # can be the entire system
}
```

The following two options have default values appropriate for the vast majority of applications, and are only provided to support rare, special cases.

- `enableFitGradients` ⟨Include the roto-translational contribution to colvar gradients⟩
  Context: atom group
  Acceptable values: boolean
  Default value: `on`
  Description: When either `centerReference` or `rotateReference` is on, the gradients of some colvars include terms proportional to $\partial R/\partial \mathbf{x}_i$ (rotational gradients) and $\partial \mathbf{x}^{\mathrm{C}}/\partial \mathbf{x}_i$ (translational gradients). By default, these terms are calculated and included in the total gradients; if this option is set to `off`, they are neglected. In the case of a minimum RMSD component, this flag is automatically disabled because the contributions of those derivatives to the gradients cancel out.

- `enableForces` ⟨Apply forces from this colvar to this group⟩
  Context: atom group
  Acceptable values: boolean
  Default value: `on`
  Description: If this option is `off`, no forces are applied from this colvar to this group. Other forces are not affected (i.e. those from the MD engine, from other colvars, and other external forces). For dummy atoms, this option is `off` by default.

4.3 Treatment of periodic boundary conditions.

In simulations with periodic boundary conditions, many of the implemented colvar components rely on the fact that each position within a group of atoms is at the nearest periodic image from the center of geometry of the group itself. However, due to the internal wrapping of individual atomic positions done by LAMMPS, this assumption is inaccurate if groups lies at one of the unit cell's boundaries. For this reason, within the Colvars module coordinates are unwrapped by default to avoid discontinuities due to coordinate wrapping (see `unwrap` keyword in 2.1).

The user should determine whether maintaining the default value of `unwrap`, depending on the specifics of each system. In general, internal coordinate wrapping by LAMMPS does not affect the calculation of colvars if each atom group satisfies one or more of the following:

i) it is composed by only one atom;

ii) it is used by a colvar component which does not make use of its center of geometry, but only of pairwise distances (`distanceInv`, `coordNum`, `hBond`, `alpha`, `dihedralPC`);

iii) it is used by a colvar component that ignores the ill-defined Cartesian components of its center of mass (such as the x and y components of a membrane's center of mass modeled with `distanceZ`).

4.4 Performance a Colvars calculation based on group size.

In simulations performed with message-passing programs (such as NAMD or LAMMPS), the calculation of energy and forces is distributed (i.e., parallelized) across multiple nodes, as well as over the processor cores of each node. Atomic coordinates are typically collected on one node, where the calculation of collective variables and of their biases is executed. This means that for simulations over large numbers of nodes, a Colvars calculation may produce a significant overhead, coming from the costs of transmitting atomic coordinates to one node and of processing them.

Performance can be improved in multiple ways:

- The calculation of variables, components and biases can be distributed over the processor cores of the node where the Colvars module is executed. Currently, an equal weight is assigned to each colvar, or to each component of those colvars that include more than one component. The performance of simulations that use many colvars or components is improved automatically. For simulations that use a single large colvar, it may be advisable to partition it in multiple components, which will be then distributed across the available cores. In LAMMPS, this feature is supported automatically. If printed, the message "SMP parallelism is available." indicates the availability of the option.

- As a general rule, the size of atom groups should be kept relatively small (up to a few thousands of atoms, depending on the size of the entire system in comparison). To gain an estimate of the computational cost of a large colvar, one can use a test calculation of the same colvar in VMD (hint: use the `time` Tcl command to measure the cost of running `cv update`).

5 Collective variable components (basis functions)

Each colvar is defined by one or more *components* (typically only one). Each component consists of a keyword identifying a functional form, and a definition block following that keyword, specifying the atoms involved and any additional parameters (cutoffs, "reference" values, ...).

The types of the components used in a colvar determine the properties of that colvar, and which biasing or analysis methods can be applied. In most cases, the colvar returns a real number, which is computed by one or more instances of the following components:

- `distance`: distance between two groups;
- `distanceZ`: projection of a distance vector on an axis;
- `distanceXY`: projection of a distance vector on a plane;
- `distanceInv`: mean distance between two groups of atoms (e.g. NOE-based distance);
- `angle`: angle between three groups;
- `dipoleAngle`: angle between two groups and dipole of a third group;
- `coordNum`: coordination number between two groups;
- `selfCoordNum`: coordination number of atoms within a group;
- `hBond`: hydrogen bond between two atoms;
- `rmsd`: root mean square deviation (RMSD) from a set of reference coordinates;
- `eigenvector`: projection of the atomic coordinates on a vector;
- `orientationAngle`: angle of the best-fit rotation from a set of reference coordinates;
- `orientationProj`: cosine of `orientationProj`;
- `spinAngle`: projection orthogonal to an axis of the best-fit rotation from a set of reference coordinates;
- `tilt`: projection on an axis of the best-fit rotation from a set of reference coordinates;
- `gyration`: radius of gyration of a group of atoms;
- `inertia`: moment of inertia of a group of atoms;
- `inertiaZ`: moment of inertia of a group of atoms around a chosen axis;

Some components do not return scalar, but vector values. They can only be combined with vector values of the same type.

- `distanceVec`: distance vector between two groups;
- `distanceDir`: unit vector parallel to distanceVec;
- `cartesian`: vector of atomic Cartesian coordinates;
- `orientation`: best-fit rotation, expressed as a unit quaternion.

In the following, all the available component types are listed, along with their physical units and the limiting values, if any. Such limiting values can be used to define `lowerBoundary` and `upperBoundary` in the parent colvar.

For each type of component, the available configurations keywords are listed: when two components share certain keywords, the second component simply references to the documentation of the first regarding that keyword. The keywords that are available for all types of components are listed at the end (see

5.1 List of available colvar components

5.1.1 `distance`: center-of-mass distance between two groups.

The `distance` `{...}` block defines a distance component between the two atom groups, `group1` and `group2`.

List of keywords (see also 5.4 for additional options):

- `group1` ⟨First group of atoms⟩
  Context: `distance`
  Acceptable values: Block `group1` `{...}`
  Description: First group of atoms.

- `group2`: analogous to `group1`

- `forceNoPBC` ⟨Calculate absolute rather than minimum-image distance?⟩
  Context: `distance`
  Acceptable values: boolean
  Default value: `no`
  Description: By default, in calculations with periodic boundary conditions, the `distance` component returns the distance according to the minimum-image convention. If this parameter is set to `yes`, PBC will be ignored and the distance between the coordinates as maintained internally will be used. This is only useful in a limited number of special cases, e.g. to describe the distance between remote points of a single macromolecule, which cannot be split across periodic cell boundaries, and for which the minimum-image distance might give the wrong result because of a relatively small periodic cell.

- `oneSiteTotalForce` ⟨Measure total force on group 1 only?⟩
  Context: `angle`, `dipoleAngle`, `dihedral`
  Acceptable values: boolean
  Default value: `no`
  Description: If this is set to `yes`, the total force is measured along a vector field (see equation (15) in section 6.1) that only involves atoms of `group1`. This option is only useful for ABF, or custom biases that compute total forces. See section 6.1 for details.

The value returned is a positive number (in Å), ranging from 0 to the largest possible interatomic distance within the chosen boundary conditions (with PBCs, the minimum image convention is used unless the `forceNoPBC` option is set).

5.1.2 `distanceZ`: projection of a distance vector on an axis.

The `distanceZ` `{...}` block defines a distance projection component, which can be seen as measuring the distance between two groups projected onto an axis, or the position of a group along such an axis. The axis can be defined using either one reference group and a constant vector, or dynamically based on two reference groups.

List of keywords (see also 5.4 for additional options):

- `main` ⟨Main group of atoms⟩
  Context: `distanceZ`
  Acceptable values: Block `main` {...}
  Description: Group of atoms whose position r is measured.

- `ref` ⟨Reference group of atoms⟩
  Context: `distanceZ`
  Acceptable values: Block `ref` {...}
  Description: Reference group of atoms. The position of its center of mass is noted r_1 below.

- `ref2` ⟨Secondary reference group⟩
  Context: `distanceZ`
  Acceptable values: Block `ref2` {...}
  Default value: none
  Description: Optional group of reference atoms, whose position r_2 can be used to define a dynamic projection axis: $e = (\|r_2 - r_1\|)^{-1} \times (r_2 - r_1)$. In this case, the origin is $r_m = 1/2(r_1 + r_2)$, and the value of the component is $e \cdot (r - r_m)$.

- `axis` ⟨Projection axis (Å)⟩
  Context: `distanceZ`
  Acceptable values: `(x, y, z)` triplet
  Default value: `(0.0, 0.0, 1.0)`
  Description: The three components of this vector define a projection axis e for the distance vector $r - r_1$ joining the centers of groups `ref` and `main`. The value of the component is then $e \cdot (r - r_1)$. The vector should be written as three components separated by commas and enclosed in parentheses.

- `forceNoPBC`: see definition of `forceNoPBC` in sec. 5.1.1 (`distance` component)

- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

This component returns a number (in Å) whose range is determined by the chosen boundary conditions. For instance, if the z axis is used in a simulation with periodic boundaries, the returned value ranges between $-b_z/2$ and $b_z/2$, where b_z is the box length along z (this behavior is disabled if `forceNoPBC` is set).

5.1.3 `distanceXY`: modulus of the projection of a distance vector on a plane.

The `distanceXY` {...} block defines a distance projected on a plane, and accepts the same keywords as the component `distanceZ`, i.e. `main`, `ref`, either `ref2` or `axis`, and `oneSiteTotalForce`. It returns the norm of the projection of the distance vector between `main` and `ref` onto the plane orthogonal to the axis. The axis is defined using the `axis` parameter or as the vector joining `ref` and `ref2` (see `distanceZ` above).
List of keywords (see also 5.4 for additional options):

- `main`: see definition of `main` in sec. 5.1.2 (`distanceZ` component)

- `ref`: see definition of `ref` in sec. 5.1.2 (`distanceZ` component)

- `ref2`: see definition of `ref2` in sec. 5.1.2 (`distanceZ` component)

- `axis`: see definition of `axis` in sec. 5.1.2 (`distanceZ` component)

- `forceNoPBC`: see definition of `forceNoPBC` in sec. 5.1.1 (`distance` component)

- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.4 `distanceVec`: distance vector between two groups.

The `distanceVec` {...} block defines a distance vector component, which accepts the same keywords as the component `distance`: `group1`, `group2`, and `forceNoPBC`. Its value is the 3-vector joining the centers of mass of `group1` and `group2`.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.5 `distanceDir`: distance unit vector between two groups.

The `distanceDir` {...} block defines a distance unit vector component, which accepts the same keywords as the component `distance`: `group1`, `group2`, and `forceNoPBC`. It returns a 3-dimensional unit vector $\mathbf{d} = (d_x, d_y, d_z)$, with $|\mathbf{d}| = 1$.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.6 `distanceInv`: mean distance between two groups of atoms.

The `distanceInv` {...} block defines a generalized mean distance between two groups of atoms 1 and 2, weighted with exponent $1/n$:

$$d_{1,2}^{[n]} = \left(\frac{1}{N_1 N_2} \sum_{i,j} \left(\frac{1}{\|\mathbf{d}^{ij}\|} \right)^n \right)^{-1/n} \tag{2}$$

where $\|\mathbf{d}^{ij}\|$ is the distance between atoms i and j in groups 1 and 2 respectively, and n is an even integer.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)
- `exponent` ⟨Exponent n in equation 2⟩
  Context: `distanceInv`
  Acceptable values: positive even integer
  Default value: 6
  Description: Defines the exponent to which the individual distances are elevated before averaging. The default value of 6 is useful for example to applying restraints based on NOE-measured distances.

This component returns a number in Å, ranging from 0 to the largest possible distance within the chosen boundary conditions.

5.1.7 `distancePairs`: set of pairwise distances between two groups.

The `distancePairs` {...} block defines a $N_1 \times N_2$-dimensional variable that includes all mutual distances between the atoms of two groups. This can be useful, for example, to develop a new variable defined over two groups, by using the `scriptedFunction` feature.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `forceNoPBC`: see definition of `forceNoPBC` in sec. 5.1.1 (`distance` component)

This component returns a $N_1 \times N_2$-dimensional vector of numbers, each ranging from 0 to the largest possible distance within the chosen boundary conditions.

5.1.8 `cartesian`: vector of atomic Cartesian coordinates.

The `cartesian` {...} block defines a component returning a flat vector containing the Cartesian coordinates of all participating atoms, in the order $(x_1, y_1, z_1, \cdots, x_n, y_n, z_n)$.
List of keywords (see also 5.4 for additional options):

- `atoms` ⟨Group of atoms⟩
  Context: `cartesian`
  Acceptable values: Block `atoms` {...}
  Description: Defines the atoms whose coordinates make up the value of the component. If `rotateReference` or `centerReference` are defined, coordinates are evaluated within the moving frame of reference.

5.1.9 `angle`: angle between three groups.

The `angle` {...} block defines an angle, and contains the three blocks `group1`, `group2` and `group3`, defining the three groups. It returns an angle (in degrees) within the interval $[0 : 180]$.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `group3`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.10 `dipoleAngle`: angle between two groups and dipole of a third group.

The `dipoleAngle` {...} block defines an angle, and contains the three blocks `group1`, `group2` and `group3`, defining the three groups, being `group1` the group where dipole is calculated. It returns an angle (in degrees) within the interval $[0 : 180]$.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `group3`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.11 `dihedral`: torsional angle between four groups.

The `dihedral {...}` block defines a torsional angle, and contains the blocks `group1`, `group2`, `group3` and `group4`, defining the four groups. It returns an angle (in degrees) within the interval $[-180:180]$. The Colvars module calculates all the distances between two angles taking into account periodicity. For instance, reference values for restraints or range boundaries can be defined by using any real number of choice.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `group3`: analogous to `group1`
- `group4`: analogous to `group1`
- `oneSiteTotalForce`: see definition of `oneSiteTotalForce` in sec. 5.1.1 (`distance` component)

5.1.12 `coordNum`: coordination number between two groups.

The `coordNum {...}` block defines a coordination number (or number of contacts), which calculates the function $(1-(d/d_0)^n)/(1-(d/d_0)^m)$, where d_0 is the "cutoff" distance, and n and m are exponents that can control its long range behavior and stiffness [2]. This function is summed over all pairs of atoms in `group1` and `group2`:

$$C(\texttt{group1},\texttt{group2}) = \sum_{i\in\texttt{group1}} \sum_{j\in\texttt{group2}} \frac{1-(|\mathbf{x}_i-\mathbf{x}_j|/d_0)^n}{1-(|\mathbf{x}_i-\mathbf{x}_j|/d_0)^m} \tag{3}$$

List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.1 (`distance` component)
- `group2`: analogous to `group1`
- `cutoff` ⟨"Interaction" distance (Å)⟩
  Context: `coordNum`
  Acceptable values: positive decimal
  Default value: 4.0
  Description: This number defines the switching distance to define an interatomic contact: for $d \ll d_0$, the switching function $(1-(d/d_0)^n)/(1-(d/d_0)^m)$ is close to 1, at $d = d_0$ it has a value of n/m (1/2 with the default n and m), and at $d \gg d_0$ it goes to zero approximately like d^{m-n}. Hence, for a proper behavior, m must be larger than n.
- `cutoff3` ⟨Reference distance vector (Å)⟩
  Context: `coordNum`
  Acceptable values: "`(x, y, z)`" triplet of positive decimals
  Default value: `(4.0, 4.0, 4.0)`
  Description: The three components of this vector define three different cutoffs d_0 for each direction. This option is mutually exclusive with `cutoff`.
- `expNumer` ⟨Numerator exponent⟩
  Context: `coordNum`
  Acceptable values: positive even integer
  Default value: 6
  Description: This number defines the n exponent for the switching function.

- `expDenom` ⟨Denominator exponent⟩
  Context: `coordNum`
  Acceptable values: positive even integer
  Default value: 12
  Description: This number defines the m exponent for the switching function.

- `group2CenterOnly` ⟨Use only `group2`'s center of mass⟩
  Context: `coordNum`
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is `on`, only contacts between each atoms in `group1` and the center of mass of `group2` are calculated (by default, the sum extends over all pairs of atoms in `group1` and `group2`). If `group2` is a `dummyAtom`, this option is set to `yes` by default.

This component returns a dimensionless number, which ranges from approximately 0 (all interatomic distances are much larger than the cutoff) to $N_{\texttt{group1}} \times N_{\texttt{group2}}$ (all distances are less than the cutoff), or $N_{\texttt{group1}}$ if `group2CenterOnly` is used. For performance reasons, at least one of `group1` and `group2` should be of limited size or `group2CenterOnly` should be used: the cost of the loop over all pairs grows as $N_{\texttt{group1}} \times N_{\texttt{group2}}$.

5.1.13 `selfCoordNum`: coordination number between atoms within a group.

The `selfCoordNum` {...} block defines a coordination number similarly to the component `coordNum`, but the function is summed over atom pairs within `group1`:

$$C(\texttt{group1}) = \sum_{i \in \texttt{group1}} \sum_{j>i} \frac{1-(|\mathbf{x}_i - \mathbf{x}_j|/d_0)^n}{1-(|\mathbf{x}_i - \mathbf{x}_j|/d_0)^m} \tag{4}$$

The keywords accepted by `selfCoordNum` are a subset of those accepted by `coordNum`, namely `group1` (here defining *all* of the atoms to be considered), `cutoff`, `expNumer`, and `expDenom`.
List of keywords (see also 5.4 for additional options):

- `group1`: see definition of `group1` in sec. 5.1.12 (`coordNum` component)
- `cutoff`: see definition of `cutoff` in sec. 5.1.12 (`coordNum` component)
- `cutoff3`: see definition of `cutoff3` in sec. 5.1.12 (`coordNum` component)
- `expNumer`: see definition of `expNumer` in sec. 5.1.12 (`coordNum` component)
- `expDenom`: see definition of `expDenom` in sec. 5.1.12 (`coordNum` component)

This component returns a dimensionless number, which ranges from approximately 0 (all interatomic distances much larger than the cutoff) to $N_{\texttt{group1}} \times (N_{\texttt{group1}} - 1)/2$ (all distances within the cutoff). For performance reasons, `group1` should be of limited size, because the cost of the loop over all pairs grows as $N^2_{\texttt{group1}}$.

5.1.14 `hBond`: hydrogen bond between two atoms.

The `hBond` {...} block defines a hydrogen bond, implemented as a coordination number (eq. 3) between the donor and the acceptor atoms. Therefore, it accepts the same options `cutoff` (with a different default value of 3.3 Å), `expNumer` (with a default value of 6) and `expDenom` (with a default value of 8). Unlike

coordNum, it requires two atom numbers, acceptor and donor, to be defined. It returns an adimensional number, with values between 0 (acceptor and donor far outside the cutoff distance) and 1 (acceptor and donor much closer than the cutoff).
List of keywords (see also 5.4 for additional options):

- acceptor ⟨Number of the acceptor atom⟩
  Context: hBond
  Acceptable values: positive integer
  Description: Number that uses the same convention as atomNumbers.
- donor: analogous to acceptor
- cutoff: see definition of cutoff in sec. 5.1.12 (coordNum component)
  Note: default value is 3.3 Å.
- expNumer: see definition of expNumer in sec. 5.1.12 (coordNum component)
  Note: default value is 6.
- expDenom: see definition of expDenom in sec. 5.1.12 (coordNum component)
  Note: default value is 8.

5.1.15 rmsd: root mean square displacement (RMSD) from reference positions.

The block rmsd {...} defines the root mean square replacement (RMSD) of a group of atoms with respect to a reference structure. For each set of coordinates $\{\mathbf{x}_1(t), \mathbf{x}_2(t), \ldots \mathbf{x}_N(t)\}$, the colvar component rmsd calculates the optimal rotation $U^{\{\mathbf{x}_i(t)\}\to\{\mathbf{x}_i^{(\mathrm{ref})}\}}$ that best superimposes the coordinates $\{\mathbf{x}_i(t)\}$ onto a set of reference coordinates $\{\mathbf{x}_i^{(\mathrm{ref})}\}$. Both the current and the reference coordinates are centered on their centers of geometry, $\mathbf{x}_{\mathrm{cog}}(t)$ and $\mathbf{x}_{\mathrm{cog}}^{(\mathrm{ref})}$. The root mean square displacement is then defined as:

$$\mathrm{RMSD}(\{\mathbf{x}_i(t)\}, \{\mathbf{x}_i^{(\mathrm{ref})}\}) \;=\; \sqrt{\frac{1}{N}\sum_{i=1}^{N} \left| U\left(\mathbf{x}_i(t) - \mathbf{x}_{\mathrm{cog}}(t)\right) - \left(\mathbf{x}_i^{(\mathrm{ref})} - \mathbf{x}_{\mathrm{cog}}^{(\mathrm{ref})}\right)\right|^2} \tag{5}$$

The optimal rotation $U^{\{\mathbf{x}_i(t)\}\to\{\mathbf{x}_i^{(\mathrm{ref})}\}}$ is calculated within the formalism developed in reference [3], which guarantees a continuous dependence of $U^{\{\mathbf{x}_i(t)\}\to\{\mathbf{x}_i^{(\mathrm{ref})}\}}$ with respect to $\{\mathbf{x}_i(t)\}$.
List of keywords (see also 5.4 for additional options):

- atoms ⟨Atom group⟩
  Context: rmsd
  Acceptable values: atoms {...} block
  Description: Defines the group of atoms of which the RMSD should be calculated. Optimal fit options (such as refPositions and rotateReference) should typically NOT be set within this block. Exceptions to this rule are the special cases discussed in the *Advanced usage* paragraph below.
- refPositions ⟨Reference coordinates⟩
  Context: rmsd
  Acceptable values: space-separated list of (x, y, z) triplets
  Description: This option (mutually exclusive with refPositionsFile) sets the reference coordinates. If only centerReference is on, the list can be a single (x, y, z) triplet; if also rotateReference is on, the list should be as long as the atom group. This option is independent from that with the same keyword within the atoms {...} block (see 4.2). The latter (and related fitting options for the atom group) are normally not needed, and should be omitted altogether except for advanced usage cases.

- `refPositionsFile` ⟨Reference coordinates file⟩
  Context: `rmsd`
  Acceptable values: UNIX filename
  Description: This option (mutually exclusive with `refPositions`) sets the file name for the reference coordinates to be compared with. The format is the same as that provided by `refPositionsFile` within an atom group's definition (see 4.2).

This component returns a positive real number (in Å).

5.1.16 Advanced usage of the `rmsd` component.

In the standard usage as described above, the `rmsd` component calculates a minimum RMSD, that is, current coordinates are optimally fitted onto the same reference coordinates that are used to compute the RMSD value. The fit itself is handled by the atom group object, whose parameters are automatically set by the `rmsd` component. For very specific applications, however, it may be useful to control the fitting process separately from the definition of the reference coordinates, to evaluate various types of non-minimal RMSD values. This can be achieved by setting the related options (`refPositions`, etc.) explicitly in the atom group block. This allows for the following non-standard cases:

1. applying the optimal translation, but no rotation (`rotateReference off`), to bias or restrain the shape and orientation, but not the position of the atom group;
2. applying the optimal rotation, but no translation (`translateReference off`), to bias or restrain the shape and position, but not the orientation of the atom group;
3. disabling the application of optimal roto-translations, which lets the RMSD component decribe the deviation of atoms from fixed positions in the laboratory frame: this allows for custom positional restraints within the Colvars module;
4. fitting the atomic positions to different reference coordinates than those used in the RMSD calculation itself;
5. applying the optimal rotation and/or translation from a separate atom group, defined through `fittingGroup`: the RMSD then reflects the deviation from reference coordinates in a separate, moving reference frame.

5.1.17 `eigenvector`: projection of the atomic coordinates on a vector.

The block `eigenvector { ... }` defines the projection of the coordinates of a group of atoms (or more precisely, their deviations from the reference coordinates) onto a vector in $\mathbb{R}^{3n}$, where n is the number of atoms in the group. The computed quantity is the total projection:

$$p(\{\mathbf{x}_i(t)\},\{\mathbf{x}_i^{(\mathrm{ref})}\}) \;=\; \sum_{i=1}^{n} \mathbf{v}_i \cdot \left(U(\mathbf{x}_i(t) - \mathbf{x}_{\mathrm{cog}}(t)) - (\mathbf{x}_i^{(\mathrm{ref})} - \mathbf{x}_{\mathrm{cog}}^{(\mathrm{ref})}) \right), \tag{6}$$

where, as in the `rmsd` component, U is the optimal rotation matrix, $\mathbf{x}_{\mathrm{cog}}(t)$ and $\mathbf{x}_{\mathrm{cog}}^{(\mathrm{ref})}$ are the centers of geometry of the current and reference positions respectively, and $\mathbf{v}_i$ are the components of the vector for each atom. Example choices for $(\mathbf{v}_i)$ are an eigenvector of the covariance matrix (essential mode), or a normal mode of the system. It is assumed that $\sum_i \mathbf{v}_i = 0$: otherwise, the Colvars module centers the $\mathbf{v}_i$ automatically when reading them from the configuration.
List of keywords (see also 5.4 for additional options):

- `atoms:` see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions:` see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile:` see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)
- `vector` ⟨Vector components⟩
  Context: `eigenvector`
  Acceptable values: space-separated list of `(x, y, z)` triplets
  Description: This option sets the values of the vector components.
- `differenceVector` ⟨The $3n$-dimensional vector is the difference between `vector` and `refPositions`⟩
  Context: `eigenvector`
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is `on`, the numbers provided by `vector` are interpreted as another set of positions, $\mathbf{x}'_i$: the vector $\mathbf{v}_i$ is then defined as $\mathbf{v}_i = \left(\mathbf{x}'_i - \mathbf{x}_i^{(\mathrm{ref})}\right)$. This allows to conveniently define a colvar ξ as a projection on the linear transformation between two sets of positions, "A" and "B". For convenience, the vector is also normalized so that $\xi = 0$ when the atoms are at the set of positions "A" and $\xi = 1$ at the set of positions "B".

This component returns a number (in Å), whose value ranges between the smallest and largest absolute positions in the unit cell during the simulations (see also `distanceZ`). Due to the normalization in eq. 6, this range does not depend on the number of atoms involved.

5.1.18 `gyration`: radius of gyration of a group of atoms.

The block `gyration` $\{\ldots\}$ defines the parameters for calculating the radius of gyration of a group of atomic positions $\{\mathbf{x}_1(t), \mathbf{x}_2(t), \ldots \mathbf{x}_N(t)\}$ with respect to their center of geometry, $\mathbf{x}_{\mathrm{cog}}(t)$:

$$R_{\mathrm{gyr}} = \sqrt{\frac{1}{N}\sum_{i=1}^{N} \left|\mathbf{x}_i(t) - \mathbf{x}_{\mathrm{cog}}(t)\right|^2} \tag{7}$$

This component must contain one `atoms` $\{\ldots\}$ block to define the atom group, and returns a positive number, expressed in Å.
List of keywords (see also 5.4 for additional options):

- `atoms:` see definition of `atoms` in sec. 5.1.15 (`rmsd` component)

5.1.19 `inertia`: total moment of inertia of a group of atoms.

The block `inertia` $\{\ldots\}$ defines the parameters for calculating the total moment of inertia of a group of atomic positions $\{\mathbf{x}_1(t), \mathbf{x}_2(t), \ldots \mathbf{x}_N(t)\}$ with respect to their center of geometry, $\mathbf{x}_{\mathrm{cog}}(t)$:

$$I = \sum_{i=1}^{N} \left|\mathbf{x}_i(t) - \mathbf{x}_{\mathrm{cog}}(t)\right|^2 \tag{8}$$

Note that all atomic masses are set to 1 for simplicity. This component must contain one `atoms` $\{\ldots\}$ block to define the atom group, and returns a positive number, expressed in Å^2.
List of keywords (see also 5.4 for additional options):

- `atoms:` see definition of `atoms` in sec. 5.1.15 (`rmsd` component)

5.1.20 `inertiaZ`: total moment of inertia of a group of atoms around a chosen axis.

The block `inertiaZ {...}` defines the parameters for calculating the component along the axis **e** of the moment of inertia of a group of atomic positions $\{\mathbf{x}_1(t), \mathbf{x}_2(t), \ldots \mathbf{x}_N(t)\}$ with respect to their center of geometry, $\mathbf{x}_{\mathrm{cog}}(t)$:

$$I_{\mathbf{e}} = \sum_{i=1}^{N} \left(\left(\mathbf{x}_i(t) - \mathbf{x}_{\mathrm{cog}}(t) \right) \cdot \mathbf{e} \right)^2 \tag{9}$$

Note that all atomic masses are set to 1 for simplicity. This component must contain one `atoms {...}` block to define the atom group, and returns a positive number, expressed in Å^2.
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `axis` ⟨Projection axis (Å)⟩
  Context: `inertiaZ`
  Acceptable values: `(x, y, z)` triplet
  Default value: `(0.0, 0.0, 1.0)`
  Description: The three components of this vector define (when normalized) the projection axis **e**.

5.1.21 `orientation`: orientation from reference coordinates.

The block `orientation {...}` returns the same optimal rotation used in the `rmsd` component to superimpose the coordinates $\{\mathbf{x}_i(t)\}$ onto a set of reference coordinates $\{\mathbf{x}_i^{(\mathrm{ref})}\}$. Such component returns a four dimensional vector $\mathtt{q} = (q_0, q_1, q_2, q_3)$, with $\sum_i q_i^2 = 1$; this *quaternion* expresses the optimal rotation $\{\mathbf{x}_i(t)\} \rightarrow \{\mathbf{x}_i^{(\mathrm{ref})}\}$ according to the formalism in reference [3]. The quaternion (q_0, q_1, q_2, q_3) can also be written as $(\cos(\theta/2), \sin(\theta/2)\mathbf{u})$, where θ is the angle and **u** the normalized axis of rotation; for example, a rotation of 90° around the z axis is expressed as "`(0.707, 0.0, 0.0, 0.707)`". The script `quaternion2rmatrix.tcl` provides Tcl functions for converting to and from a 4×4 rotation matrix in a format suitable for usage in VMD.

As for the component `rmsd`, the available options are `atoms`, `refPositionsFile` and `refPositions`.

Note: `refPositions`and `refPositionsFile` define the set of positions *from which* the optimal rotation is calculated, but this rotation is not applied to the coordinates of the atoms involved: it is used instead to define the variable itself.
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions`: see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile`: see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)
- `closestToQuaternion` ⟨Reference rotation⟩
  Context: `orientation`
  Acceptable values: "`(q0, q1, q2, q3)`" quadruplet
  Default value: `(1.0, 0.0, 0.0, 0.0)` ("null" rotation)
  Description: Between the two equivalent quaternions (q_0, q_1, q_2, q_3) and $(-q_0, -q_1, -q_2, -q_3)$, the closer to `(1.0, 0.0, 0.0, 0.0)` is chosen. This simplifies the visualization of the colvar trajectory when samples values are a smaller subset of all possible rotations. **Note:** *this only affects the output, never the dynamics.*

Tip: stopping the rotation of a protein. To stop the rotation of an elongated macromolecule in solution (and use an anisotropic box to save water molecules), it is possible to define a colvar with an `orientation` component, and restrain it throuh the `harmonic` bias around the identity rotation, `(1.0, 0.0, 0.0, 0.0)`. Only the overall orientation of the macromolecule is affected, and *not* its internal degrees of freedom. The user should also take care that the macromolecule is composed by a single chain, or disable `wrapAll` otherwise.

5.1.22 `orientationAngle`: angle of rotation from reference coordinates.

The block `orientationAngle` {...} accepts the same base options as the component `orientation`: `atoms`, `refPositions`, `refPositionsFile`. The returned value is the angle of rotation θ between the current and the reference positions. This angle is expressed in degrees within the range [0°:180°].
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions`: see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile`: see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)

5.1.23 `orientationProj`: cosine of the angle of rotation from reference coordinates.

The block `orientationProj` {...} accepts the same base options as the component `orientation`: `atoms`, `refPositions`, `refPositionsFile`. The returned value is the cosine of the angle of rotation θ between the current and the reference positions. The range of values is [-1:1].
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions`: see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile`: see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)

5.1.24 `spinAngle`: angle of rotation around a given axis.

The complete rotation described by `orientation` can optionally be decomposed into two sub-rotations: one is a "*spin*" rotation around **e**, and the other a "*tilt*" rotation around an axis orthogonal to **e**. The component `spinAngle` measures the angle of the "spin" sub-rotation around **e**.
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions`: see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile`: see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)
- `axis` ⟨Special rotation axis (Å)⟩
  Context: `tilt`
  Acceptable values: `(x, y, z)` triplet
  Default value: `(0.0, 0.0, 1.0)`
  Description: The three components of this vector define (when normalized) the special rotation axis used to calculate the `tilt` and `spinAngle` components.

The component `spinAngle` returns an angle (in degrees) within the periodic interval $[-180 : 180]$.

Note: the value of `spinAngle` is a continuous function almost everywhere, with the exception of configurations with the corresponding "tilt" angle equal to 180° (i.e. the `tilt` component is equal to -1): in those cases, `spinAngle` is undefined. If such configurations are expected, consider defining a `tilt` colvar using the same axis **e**, and restraining it with a lower wall away from -1.

5.1.25 `tilt`: cosine of the rotation orthogonal to a given axis.

The component `tilt` measures the cosine of the angle of the "tilt" sub-rotation, which combined with the "spin" sub-rotation provides the complete rotation of a group of atoms. The cosine of the tilt angle rather than the tilt angle itself is implemented, because the latter is unevenly distributed even for an isotropic system: consider as an analogy the angle θ in the spherical coordinate system. The component `tilt` relies on the same options as `spinAngle`, including the definition of the axis **e**. The values of `tilt` are real numbers in the interval $[-1 : 1]$: the value 1 represents an orientation fully parallel to **e** (tilt angle = 0°), and the value -1 represents an anti-parallel orientation.
List of keywords (see also 5.4 for additional options):

- `atoms`: see definition of `atoms` in sec. 5.1.15 (`rmsd` component)
- `refPositions`: see definition of `refPositions` in sec. 5.1.15 (`rmsd` component)
- `refPositionsFile`: see definition of `refPositionsFile` in sec. 5.1.15 (`rmsd` component)
- `axis`: see definition of `axis` in sec. 5.1.24 (`spinAngle` component)

5.2 Configuration keywords shared by all components

The following options can be used for any of the above colvar components in order to obtain a polynomial combination.

- `name` ⟨Name of this component⟩
  Context: any component
  Acceptable values: string
  Default value: type of component + numeric id
  Description: The name is an unique case-sensitive string which allows the Colvars module to identify this component. This is useful, for example, when combining multiple components via a `scriptedFunction`.

- `scalable` ⟨Attempt to calculate this component in parallel?⟩
  Context: any component
  Acceptable values: boolean
  Default value: on, if available
  Description: If set to on (default), the Colvars module will attempt to calculate this component in parallel to reduce overhead. Whether this option is available depends on the type of component: currently supported are `distance`, `distanceZ`, `distanceXY`, `distanceVec`, `distanceDir`, `angle` and `dihedral`. This flag influences computational cost, but does not affect numerical results: therefore, it should only be turned off for debugging or testing purposes.

5.3 Advanced usage and special considerations

5.3.1 Periodic components.

The following components returns real numbers that lie in a periodic interval:

- `dihedral`: torsional angle between four groups;
- `spinAngle`: angle of rotation around a predefined axis in the best-fit from a set of reference coordinates.

In certain conditions, `distanceZ` can also be periodic, namely when periodic boundary conditions (PBCs) are defined in the simulation and `distanceZ`'s axis is parallel to a unit cell vector.

The following keywords can be used within periodic components (and are illegal elsewhere):

- `period` ⟨Period of the component⟩
  Context: `distanceZ`
  Acceptable values: positive decimal
  Default value: 0.0
  Description: Setting this number enables the treatment of `distanceZ` as a periodic component: by default, `distanceZ` is not considered periodic. The keyword is supported, but irrelevant within `dihedral` or `spinAngle`, because their period is always 360 degrees.

- `wrapAround` ⟨Center of the wrapping interval for periodic variables⟩
  Context: `distanceZ`, `dihedral` or `spinAngle`
  Acceptable values: decimal
  Default value: 0.0
  Description: By default, values of the periodic components are centered around zero, ranging from $-P/2$ to $P/2$, where P is the period. Setting this number centers the interval around this value. This can be useful for convenience of output, or to set `lowerWall` and `upperWall` in an order that would not otherwise be allowed.

Internally, all differences between two values of a periodic colvar follow the minimum image convention: they are calculated based on the two periodic images that are closest to each other.

Note: linear or polynomial combinations of periodic components may become meaningless when components cross the periodic boundary. Use such combinations carefully: estimate the range of possible values of each component in a given simulation, and make use of `wrapAround` *to limit this problem whenever possible.*

5.3.2 Non-scalar components.

When one of the following components are used, the defined colvar returns a value that is not a scalar number:

- `distanceVec`: 3-dimensional vector of the distance between two groups;
- `distanceDir`: 3-dimensional unit vector of the distance between two groups;
- `orientation`: 4-dimensional unit quaternion representing the best-fit rotation from a set of reference coordinates.

The distance between two 3-dimensional unit vectors is computed as the angle between them. The distance between two quaternions is computed as the angle between the two 4-dimensional unit vectors: because the orientation represented by `q` is the same as the one represented by $-$`q`, distances between two quaternions are computed considering the closest of the two symmetric images.

Non-scalar components carry the following restrictions:

- Calculation of total forces (`outputTotalForce` option) is currently not implemented.
- Each colvar can only contain one non-scalar component.
- Binning on a grid (`abf`, `histogram` and `metadynamics` with `useGrids` enabled) is currently not implemented for colvars based on such components.

Note: while these restrictions apply to individual colvars based on non-scalar components, no limit is set to the number of scalar colvars. To compute multi-dimensional histograms and PMFs, use sets of scalar colvars of arbitrary size.

5.3.3 Calculating total forces.

In addition to the restrictions due to the type of value computed (scalar or non-scalar), a final restriction can arise when calculating total force (`outputTotalForce` option or application of a `abf` bias). total forces are available currently only for the following components: `distance`, `distanceZ`, `distanceXY`, `angle`, `dihedral`, `rmsd`, `eigenvector` and `gyration`.

5.4 Linear and polynomial combinations of components

To extend the set of possible definitions of colvars $\xi(\mathbf{r})$, multiple components $q_i(\mathbf{r})$ can be summed with the formula:

$$\xi(\mathbf{r}) = \sum_i c_i [q_i(\mathbf{r})]^{n_i} \tag{10}$$

where each component appears with a unique coefficient c_i (1.0 by default) the positive integer exponent n_i (1 by default).

Any set of components can be combined within a colvar, provided that they return the same type of values (scalar, unit vector, vector, or quaternion). By default, the colvar is the sum of its components. Linear or polynomial combinations (following equation (10)) can be obtained by setting the following parameters, which are common to all components:

- `componentCoeff` ⟨Coefficient of this component in the colvar⟩
  Context: any component
  Acceptable values: decimal
  Default value: `1.0`
  Description: Defines the coefficient by which this component is multiplied (after being raised to `componentExp`) before being added to the sum.

- `componentExp` ⟨Exponent of this component in the colvar⟩
  Context: any component
  Acceptable values: integer
  Default value: `1`
  Description: Defines the power at which the value of this component is raised before being added to the sum. When this exponent is different than 1 (non-linear sum), total forces and the Jacobian force are not available, making the colvar unsuitable for ABF calculations.

Example: To define the *average* of a colvar across different parts of the system, simply define within the same colvar block a series of components of the same type (applied to different atom groups), and assign to each component a `componentCoeff` of $1/N$.

6 Biasing and analysis methods

All of the biasing and analysis methods implemented (`abf`, `harmonic`, `histogram` and `metadynamics`) recognize the following options:

- `name` ⟨Identifier for the bias⟩
  Context: colvar bias
  Acceptable values: string
  Default value: `<type of bias><bias index>`
  Description: This string is used to identify the bias or analysis method in output messages and to name some output files.

- `colvars` ⟨Collective variables involved⟩
  Context: colvar bias
  Acceptable values: space-separated list of colvar names
  Description: This option selects by name all the colvars to which this bias or analysis will be applied.

- `outputEnergy` ⟨Write the current bias energy to the trajectory file⟩
  Context: colvar bias
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is chosen and `colvarsTrajFrequency` is not zero, the current value of the biasing energy will be written to the trajectory file during the simulation.

6.1 Adaptive Biasing Force

For a full description of the Adaptive Biasing Force method, see reference [4]. For details about this implementation, see references [5] and [6]. **When publishing research that makes use of this functionality, please cite references [4] and [6].**

An alternate usage of this feature is the application of custom tabulated biasing potentials to one or more colvars. See `inputPrefix` and `updateBias` below.

Combining ABF with the extended Lagrangian feature (3.3) of the variables produces the extended-system ABF variant of the method (6.2).

ABF is based on the thermodynamic integration (TI) scheme for computing free energy profiles. The free energy as a function of a set of collective variables $\xi = (\xi_i)_{i\in[1,n]}$ is defined from the canonical distribution of ξ, $\mathscr{P}(\xi)$:

$$A(\xi) = -\frac{1}{\beta}\ln \mathscr{P}(\xi) + A_0 \tag{11}$$

In the TI formalism, the free energy is obtained from its gradient, which is generally calculated in the form of the average of a force F_ξ exerted on ξ, taken over an iso-ξ surface:

$$\nabla_\xi A(\xi) = \left\langle -F_\xi \right\rangle_\xi \tag{12}$$

Several formulae that take the form of (12) have been proposed. This implementation relies partly on the classic formulation [7], and partly on a more versatile scheme originating in a work by Ruiz-Montero et al. [8], generalized by den Otter [9] and extended to multiple variables by Ciccotti et al. [10]. Consider a system subject to constraints of the form $\sigma_k(x) = 0$. Let $(v_i)_{i\in[1,n]}$ be arbitrarily chosen vector fields ($\mathbb{R}^{3N} \to \mathbb{R}^{3N}$) verifying, for all i, j, and k:

$$v_i \cdot \nabla_x \xi_j = \delta_{ij} \tag{13}$$
$$v_i \cdot \nabla_x \sigma_k = 0 \tag{14}$$

then the following holds [10]:

$$\frac{\partial A}{\partial \xi_i} = \langle v_i \cdot \nabla_x V - k_B T \nabla_x \cdot v_i \rangle_\xi \tag{15}$$

where V is the potential energy function. v_i can be interpreted as the direction along which the force acting on variable ξ_i is measured, whereas the second term in the average corresponds to the geometric entropy contribution that appears as a Jacobian correction in the classic formalism [7]. Condition (13) states that the direction along which the total force on ξ_i is measured is orthogonal to the gradient of ξ_j, which means that the force measured on ξ_i does not act on ξ_j.

Equation (14) implies that constraint forces are orthogonal to the directions along which the free energy gradient is measured, so that the measurement is effectively performed on unconstrained degrees of freedom.

In the framework of ABF, $\mathbf{F}_\xi$ is accumulated in bins of finite size $\delta\xi$, thereby providing an estimate of the free energy gradient according to equation (12). The biasing force applied along the collective variables to overcome free energy barriers is calculated as:

$$\mathbf{F}^{\mathrm{ABF}} = \alpha(N_\xi) \times \nabla_x \widetilde{A}(\xi) \tag{16}$$

where $\nabla_x \widetilde{A}$ denotes the current estimate of the free energy gradient at the current point ξ in the collective variable subspace, and $\alpha(N_\xi)$ is a scaling factor that is ramped from 0 to 1 as the local number of samples N_ξ increases to prevent nonequilibrium effects in the early phase of the simulation, when the gradient estimate has a large variance. See the `fullSamples` parameter below for details.

As sampling of the phase space proceeds, the estimate $\nabla_x \widetilde{A}$ is progressively refined. The biasing force introduced in the equations of motion guarantees that in the bin centered around ξ, the forces acting along the selected collective variables average to zero over time. Eventually, as the undelying free energy surface is canceled by the adaptive bias, evolution of the system along ξ is governed mainly by diffusion. Although this implementation of ABF can in principle be used in arbitrary dimension, a higher-dimension collective variable space is likely to result in sampling difficulties. Most commonly, the number of variables is one or two.

6.1.1 ABF requirements on collective variables

The following conditions must be met for an ABF simulation to be possible and to produce an accurate estimate of the free energy profile. Note that these requirements do not apply when using the extended-system ABF method (6.2).

1. *Only linear combinations* of colvar components can be used in ABF calculations.

2. *Availability of total forces* is necessary. The following colvar components can be used in ABF calculations: `distance`, `distance_xy`, `distance_z`, `angle`, `dihedral`, `gyration`, `rmsd` and `eigenvector`. Atom groups may not be replaced by dummy atoms, unless they are excluded from the force measurement by specifying `oneSiteTotalForce`, if available.

3. *Mutual orthogonality of colvars*. In a multidimensional ABF calculation, equation (13) must be satisfied for any two colvars ξ_i and ξ_j. Various cases fulfill this orthogonality condition:

   - ξ_i and ξ_j are based on non-overlapping sets of atoms.
   - atoms involved in the force measurement on ξ_i do not participate in the definition of ξ_j. This can be obtained using the option `oneSiteTotalForce` of the `distance`, `angle`, and `dihedral` components (example: Ramachandran angles ϕ, ψ).
   - ξ_i and ξ_j are orthogonal by construction. Useful cases are the sum and difference of two components, or `distance_z` and `distance_xy` using the same axis.

4. *Mutual orthogonality of components*: when several components are combined into a colvar, it is assumed that their vectors v_i (equation (15)) are mutually orthogonal. The cases described for colvars in the previous paragraph apply.

5. *Orthogonality of colvars and constraints*: equation 14 can be satisfied in two simple ways, if either no constrained atoms are involved in the force measurement (see point 3 above) or pairs of atoms joined by a constrained bond are part of an *atom group* which only intervenes through its center (center of mass or geometric center) in the force measurement. In the latter case, the contributions of the two atoms to the left-hand side of equation 14 cancel out. For example, all atoms of a rigid TIP3P water molecule can safely be included in an atom group used in a `distance` component.

6.1.2 Parameters for ABF

ABF depends on parameters from collective variables to define the grid on which free energy gradients are computed. In the direction of each colvar, the grid ranges from `lowerBoundary` to `upperBoundary`, and the bin width (grid spacing) is set by the `width` parameter (see 3.1). The following specific parameters can be set in the ABF configuration block:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)

- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)

- `fullSamples` ⟨Number of samples in a bin prior to application of the ABF⟩
  Context: `abf`
  Acceptable values: positive integer
  Default value: 200
  Description: To avoid nonequilibrium effects due to large fluctuations of the force exerted along the colvars, it is recommended to apply a biasing force only after a the estimate has started converging. If `fullSamples` is non-zero, the applied biasing force is scaled by a factor $\alpha(N_\xi)$ between 0 and 1. If the number of samples N_ξ in the current bin is higher than `fullSamples`, the factor is one. If it is less than half of `fullSamples`, the factor is zero and no bias is applied. Between those two thresholds, the factor follows a linear ramp from 0 to 1: $\alpha(N_\xi) = (2N_\xi/\text{fullSamples}) - 1$.

- `maxForce` ⟨Maximum magnitude of the ABF force⟩
  Context: `abf`

Acceptable values: positive decimals (one per colvar)
Default value: disabled
Description: This option enforces a cap on the magnitude of the biasing force effectively applied by this ABF bias on each colvar. This can be useful in the presence of singularities in the PMF such as hard walls, where the discretization of the average force becomes very inaccurate, causing the colvar's diffusion to get "stuck" at the singularity. To enable this cap, provide one non-negative value for each colvar. The unit of force is the unit of energy specified by `units` divided by the colvar unit.

- `hideJacobian` ⟨Remove geometric entropy term from calculated free energy gradient?⟩
Context: `abf`
Acceptable values: boolean
Default value: `no`
Description: In a few special cases, most notably distance-based variables, an alternate definition of the potential of mean force is traditionally used, which excludes the Jacobian term describing the effect of geometric entropy on the distribution of the variable. This results, for example, in particle-particle potentials of mean force being flat at large separations. Setting this parameter to `yes` causes the output data to follow that convention, by removing this contribution from the output gradients while applying internally the corresponding correction to ensure uniform sampling. It is not allowed for colvars with multiple components.

- `outputFreq` ⟨Frequency (in timesteps) at which ABF data files are refreshed⟩
Context: `abf`
Acceptable values: positive integer
Default value: Colvars module restart frequency
Description: The files containing the free energy gradient estimate and sampling histogram (and the PMF in one-dimensional calculations) are written on disk at the given time interval.

- `historyFreq` ⟨Frequency (in timesteps) at which ABF history files are accumulated⟩
Context: `abf`
Acceptable values: positive integer
Default value: 0
Description: If this number is non-zero, the free energy gradient estimate and sampling histogram (and the PMF in one-dimensional calculations) are appended to files on disk at the given time interval. History file names use the same prefix as output files, with "`.hist`" appended.

- `inputPrefix` ⟨Filename prefix for reading ABF data⟩
Context: `abf`
Acceptable values: list of strings
Description: If this parameter is set, for each item in the list, ABF tries to read a gradient and a sampling files named `<inputPrefix>.grad` and `<inputPrefix>.count`. This is done at startup and sets the initial state of the ABF algorithm. The data from all provided files is combined appropriately. Also, the grid definition (min and max values, width) need not be the same that for the current run. This command is useful to piece together data from simulations in different regions of collective variable space, or change the colvar boundary values and widths. Note that it is not recommended to use it to switch to a smaller width, as that will leave some bins empty in the finer data grid. This option is NOT compatible with reading the data from a restart file (`input` keyword of the `fix ID group-ID colvars` command).

- `applyBias` ⟨Apply the ABF bias?⟩
Context: `abf`

Acceptable values: boolean
Default value: `yes`
Description: If this is set to no, the calculation proceeds normally but the adaptive biasing force is not applied. Data is still collected to compute the free energy gradient. This is mostly intended for testing purposes, and should not be used in routine simulations.

- `updateBias` ⟨Update the ABF bias?⟩
Context: `abf`
Acceptable values: boolean
Default value: `yes`
Description: If this is set to no, the initial biasing force (e.g. read from a restart file or through `inputPrefix`) is not updated during the simulation. As a result, a constant bias is applied. This can be used to apply a custom, tabulated biasing potential to any combination of colvars. To that effect, one should prepare a gradient file containing the gradient of the potential to be applied (negative of the bias force), and a count file containing only values greater than `fullSamples`. These files must match the grid parameters of the colvars.

6.1.3 Output files

The ABF bias produces the following files, all in multicolumn text format:

- *output*`.grad`: current estimate of the free energy gradient (grid), in multicolumn;
- *output*`.count`: histogram of samples collected, on the same grid;
- *output*`.pmf`: only for one-dimensional calculations, integrated free energy profile or PMF.

If several ABF biases are defined concurrently, their name is inserted to produce unique filenames for output, as in *output*`.abf1.grad`. This should not be done routinely and could lead to meaningless results: only do it if you know what you are doing!

If the colvar space has been partitioned into sections (*windows*) in which independent ABF simulations have been run, the resulting data can be merged using the `inputPrefix` option described above (a run of 0 steps is enough).

6.1.4 Post-processing: reconstructing a multidimensional free energy surface

If a one-dimensional calculation is performed, the estimated free energy gradient is automatically integrated and a potential of mean force is written under the file name `<outputName>.pmf`, in a plain text format that can be read by most data plotting and analysis programs (e.g. gnuplot).

In dimension 2 or greater, integrating the discretized gradient becomes non-trivial. The standalone utility `abf_integrate` is provided to perform that task. `abf_integrate` reads the gradient data and uses it to perform a Monte-Carlo (M-C) simulation in discretized collective variable space (specifically, on the same grid used by ABF to discretize the free energy gradient). By default, a history-dependent bias (similar in spirit to metadynamics) is used: at each M-C step, the bias at the current position is incremented by a preset amount (the *hill height*). Upon convergence, this bias counteracts optimally the underlying gradient; it is negated to obtain the estimate of the free energy surface.

`abf_integrate` is invoked using the command-line:

```
abf_integrate <gradient_file> [-n <nsteps>] [-t <temp>] [-m (0|1)] [-h <hill_height>] [-f <factor>]
```

The gradient file name is provided first, followed by other parameters in any order. They are described below, with their default value in square brackets:

- `-n`: number of M-C steps to be performed; by default, a minimal number of steps is chosen based on the size of the grid, and the integration runs until a convergence criterion is satisfied (based on the RMSD between the target gradient and the real PMF gradient)
- `-t`: temperature for M-C sampling (unrelated to the simulation temperature) [500 K]
- `-m`: use metadynamics-like biased sampling? (0 = false) [1]
- `-h`: increment for the history-dependent bias ("hill height") [0.01 kcal/mol]
- `-f`: if non-zero, this factor is used to scale the increment stepwise in the second half of the M-C sampling to refine the free energy estimate [0.5]

Using the default values of all parameters should give reasonable results in most cases.

`abf_integrate` produces the following output files:

- `<gradient_file>.pmf`: computed free energy surface
- `<gradient_file>.histo`: histogram of M-C sampling (not usable in a straightforward way if the history-dependent bias has been applied)
- `<gradient_file>.est`: estimated gradient of the calculated free energy surface (from finite differences)
- `<gradient_file>.dev`: deviation between the user-provided numerical gradient and the actual gradient of the calculated free energy surface. The RMS norm of this vector field is used as a convergence criteria and displayed periodically during the integration.

Note: Typically, the "deviation" vector field does not vanish as the integration converges. This happens because the numerical estimate of the gradient does not exactly derive from a potential, due to numerical approximations used to obtain it (finite sampling and discretization on a grid).

6.2 Extended-system Adaptive Biasing Force (eABF)

Extended-system ABF (eABF) is a variant of ABF (6.1) where the bias is not applied directly to the collective variable, but to an extended coordinate ("fictitious variable") λ that evolves dynamically according to Newtonian or Langevin dynamics. Such an extended coordinate is enabled for a given colvar using the `extendedLagrangian` and associated keywords (3.3). The theory of eABF and the present implementation are documented in detail in reference [11].

Defining an ABF bias on a colvar wherein the `extendedLagrangian` option is active will perform eABF; there is no dedicated option.

The extended variable λ is coupled to the colvar $z = \xi(q)$ by the harmonic potential $(k/2)(z-\lambda)^2$. Under eABF dynamics, the adaptive bias on λ is the running estimate of the average spring force:

$$F^{\text{bias}}(\lambda^*) = \langle k(\lambda - z)\rangle_{\lambda^*} \tag{17}$$

where the angle brackets indicate a canonical average conditioned by $\lambda = \lambda^*$. At long simulation times, eABF produces a flat histogram of the extended variable λ, and a flattened histogram of ξ, whose exact shape depends on the strength of the coupling as defined by `extendedFluctuation` in the colvar. Coupling should be somewhat loose for faster exploration and convergence, but strong enough that the bias does help overcome barriers along the colvar ξ.[11] Distribution of the colvar may be assessed by plotting its histogram, which is written to the *output*`.zcount` file in every eABF simulation. Note that a `histogram` bias (6.8) applied to an extended-Lagrangian colvar will access the extended degree of freedom λ, not the

original colvar ξ; however, the joint histogram may be explicitly requested by listing the name of the colvar twice in a row within the `colvars` parameter of the `histogram` block.

The eABF PMF is that of the coordinate λ, it is not exactly the free energy profile of ξ. That quantity can be calculated based on the CZAR estimator.

6.2.1 CZAR estimator of the free energy

The *corrected z-averaged restraint* (CZAR) estimator is described in detail in reference [11]. It is computed automatically in eABF simulations, regardless of the number of colvars involved. Note that ABF may also be applied on a combination of extended and non-extended colvars; in that case, CZAR still provides an unbiased estimate of the free energy gradient.

CZAR estimates the free energy gradient as:

$$A'(z) = -\frac{1}{\beta}\frac{d\ln\tilde{\rho}(z)}{dz} + k(\langle\lambda\rangle_z - z). \tag{18}$$

where $z = \xi(q)$ is the colvar, λ is the extended variable harmonically coupled to z with a force constant k, and $\tilde{\rho}(z)$ is the observed distribution (histogram) of z, affected by the eABF bias.

There is only one optional parameter to the CZAR estimator:

- `writeCZARwindowFile` ⟨Write internal data from CZAR to a separate file?⟩
  Context: `abf`
  Acceptable values: boolean
  Default value: `no`
  Description: When this option is enabled, eABF simulations will write a file containing the z-averaged restraint force under the name *output*`.zgrad`. The same information is always included in the colvars state file, which is sufficient for restarting an eABF simulation. These separate file is only useful when joining adjacent windows from a stratified eABF simulation, either to continue the simulation in a broader window or to compute a CZAR estimate of the PMF over the full range of the coordinate(s).

Similar to ABF, the CZAR estimator produces two output files in multicolumn text format:

- *output*`.czar.grad`: current estimate of the free energy gradient (grid), in multicolumn;
- *output*`.czar.pmf`: only for one-dimensional calculations, integrated free energy profile or PMF.

The sampling histogram associated with the CZAR estimator is the z-histogram, which is written in the file *output*`.zcount`.

6.3 Metadynamics

The metadynamics method uses a history-dependent potential [12] that generalizes to any type of colvars the conformational flooding [13] and local elevation [14] methods, originally formulated to use as colvars the principal components of a covariance matrix or a set of dihedral angles, respectively. The metadynamics potential on the colvars $\xi = (\xi_1, \xi_2, \ldots, \xi_{N_{\text{cv}}})$ is defined as:

$$V_{\text{meta}}(\xi(t)) = \sum_{t'=\delta t, 2\delta t, \ldots}^{t'<t} W \prod_{i=1}^{N_{\text{cv}}} \exp\left(-\frac{(\xi_i(t) - \xi_i(t'))^2}{2\sigma_{\xi_i}^2}\right), \tag{19}$$

where V_{meta} is the history-dependent potential acting on the *current* values of the colvars ξ, and depends only parametrically on the *previous* values of the colvars. V_{meta} is constructed as a sum of N_{cv}-dimensional

repulsive Gaussian "hills", whose height is a chosen energy constant W, and whose centers are the previously explored configurations $(\xi(\delta t), \xi(2\delta t), \ldots)$.

During the simulation, the system evolves towards the nearest minimum of the "effective" potential of mean force $\tilde{A}(\xi)$, which is the sum of the "real" underlying potential of mean force $A(\xi)$ and the the metadynamics potential, $V_{\text{meta}}(\xi)$. Therefore, at any given time the probability of observing the configuration ξ^* is proportional to $\exp\left(-\tilde{A}(\xi^*)/\kappa_B T\right)$: this is also the probability that a new Gaussian "hill" is added at that configuration. If the simulation is run for a sufficiently long time, each local minimum is canceled out by the sum of the Gaussian "hills". At that stage the "effective" potential of mean force $\tilde{A}(\xi)$ is constant, and $-V_{\text{meta}}(\xi)$ is an accurate estimator of the "real" potential of mean force $A(\xi)$, save for an additive constant:

$$A(\xi) \simeq -V_{\text{meta}}(\xi) + K \tag{20}$$

Assuming that the set of collective variables includes all relevant degrees of freedom, the predicted error of the estimate is a simple function of the correlation times of the colvars τ_{ξ_i}, and of the user-defined parameters W, σ_{ξ_i} and δt [15]. In typical applications, a good rule of thumb can be to choose the ratio $W/\delta t$ much smaller than $\kappa_B T/\tau_\xi$, where τ_ξ is the longest among ξ's correlation times: σ_{ξ_i} then dictates the resolution of the calculated PMF.

To enable a metadynamics calculation, a `metadynamics` block must be defined in the colvars configuration file. Its mandatory keywords are `colvars`, which lists all the variables involved, and `hillWeight`, which specifies the weight parameter W. The parameters δt and σ_ξ specified by the optional keywords `newHillFrequency` and `hillWidth`:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)
- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)
- `outputEnergy`: see definition of `outputEnergy` in sec. 6 (biasing and analysis methods)
- `hillWeight` ⟨Height of each hill (unit of energy specified by `units`)⟩
  Context: `metadynamics`
  Acceptable values: positive decimal
  Description: This option sets the height W of the Gaussian hills that are added during this run. Lower values provide more accurate sampling of the system's degrees of freedom at the price of longer simulation times to complete a PMF calculation based on metadynamics.
- `newHillFrequency` ⟨Frequency of hill creation⟩
  Context: `metadynamics`
  Acceptable values: positive integer
  Default value: `1000`
  Description: This option sets the number of integration steps after which a new hill is added to the metadynamics potential. Its value determines the parameter δt in eq. 19. Higher values provide more accurate sampling at the price of longer simulation times to complete a PMF calculation.
- `hillWidth` ⟨Relative width of a Gaussian hill with respect to the colvar's width⟩
  Context: `metadynamics`
  Acceptable values: positive decimal
  Default value: $\sqrt{2\pi}/2$
  Description: The Gaussian width along each colvar, $2\sigma_{\xi_i}$, is set as the product between this number and the colvar's parameter w_i given by `width` (see 3.1); such product is printed in the standard output of LAMMPS. The default value of this number gives a Gaussian hill function whose volume is equal

to the product of $\prod_i w_i$, the volume of one `histogram` bin (see 6.8), and W. **Tip:** *use this property to estimate the fraction of colvar space covered by the Gaussian bias within a given simulation time.* When `useGrids` is on, the default value also gives acceptable discretization errors [1]: for smoother visualization, this parameter may be increased and the `width` w_i decreased in the same proportion. **Note:** *values smaller than 1 are not recommended.*

6.3.1 Output files

When interpolating grids are enabled (default behavior), the PMF is written every `colvarsRestartFrequency` steps to the file *output*`.pmf`. The following two options allow to control this behavior and to visually track statistical convergence:

- `writeFreeEnergyFile` ⟨Periodically write the PMF for visualization⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `on`
  Description: When `useGrids` and this option are `on`, the PMF is written every `colvarsRestartFrequency` steps.

- `keepFreeEnergyFiles` ⟨Keep all the PMF files⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: When `writeFreeEnergyFile` and this option are `on`, the step number is included in the file name, thus generating a series of PMF files. Activating this option can be useful to follow more closely the convergence of the simulation, by comparing PMFs separated by short times.

Note: when Gaussian hills are deposited near `lowerBoundary` or `upperBoundary` (see 3.1) and interpolating grids are used (default behavior), their truncation can give rise to accumulating errors. In these cases, as a measure of fault-tolerance all Gaussian hills near the boundaries are included in the output state file, and are recalculated analytically whenever the colvar falls outside the grid's boundaries. (Such measure protects the accuracy of the calculation, and can only be disabled by `hardLowerBoundary` or `hardUpperBoundary`.) To avoid gradual loss of performance and growth of the state file, either one of the following solutions is recommended:

- enabling the option `expandBoundaries`, so that the grid's boundaries are automatically recalculated whenever necessary; the resulting `.pmf` will have its abscissas expanded accordingly;
- setting `lowerWall` and `upperWall` well within the interval delimited by `lowerBoundary` and `upperBoundary`.

6.3.2 Performance tuning

The following options control the computational cost of metadynamics calculations, but do not affect results. Default values are chosen to minimize such cost with no loss of accuracy.

- `useGrids` ⟨Interpolate the hills with grids⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `on`

Description: This option discretizes all hills for improved performance, accumulating their energy and their gradients on two separate grids of equal spacing. Grids are defined by the values of `lowerBoundary`, `upperBoundary` and `width` for each colvar. Currently, this option is implemented for all types of variables except the non-scalar types (`distanceDir` or `orientation`). If `expandBoundaries` is defined in one of the colvars, grids are automatically expanded along the direction of that colvar.

- `rebinGrids` ⟨Recompute the grids when reading a state file⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: When restarting from a state file, the grid's parameters (boundaries and widths) saved in the state file override those in the configuration file. Enabling this option forces the grids to match those in the current configuration file.

6.3.3 Well-tempered metadynamics

The following options define the configuration for the "well-tempered" metadynamics approach [16]:

- `wellTempered` ⟨Perform well-tempered metadynamics⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: If enabled, this flag causes well-tempered metadynamics as described by Barducci et al.[16] to be performed, rather than standard metadynamics. The parameter `biasTemperature` is then required.This feature was contributed by Li Li (Luthey-Schulten group, Departement of Chemistry, UIUC).

- `biasTemperature` ⟨Temperature bias for well-tempered metadynamics⟩
  Context: `metadynamics`
  Acceptable values: positive decimal
  Description: When running metadynamics in the long time limit, collective variable space is sampled to a modified temperature $T + \Delta T$. In conventional metadynamics, the temperature "boost" ΔT would constantly increases with time. Instead, in well-tempered metadynamics ΔT must be defined by the user via `biasTemperature`. The written PMF includes the scaling factor $(T + \Delta T)/\Delta T$ [16]. A careful choice of ΔT determines the sampling and convergence rate, and is hence crucial to the success of a well-tempered metadynamics simulation.

6.3.4 Multiple-replicas metadynamics

The following options define metadynamics calculations with more than one replica:

- `multipleReplicas` ⟨Multiple replicas metadynamics⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is on, multiple (independent) replica of the same system can be run at the same time, and their hills will be combined to obtain a single PMF [17]. Replicas are identified by the value of `replicaID`. Communication is done by files: each replica must be able to read the files

created by the others, whose paths are communicated through the file `replicasRegistry`. This file, and the files listed in it, are read every `replicaUpdateFrequency` steps. Every time the colvars state file is written (`colvarsRestartFrequency`), the file:
"*output*`.colvars.`*name*`.`*replicaID*`.state`" is also written, containing the state of the metadynamics bias for `replicaID`. In the time steps between `colvarsRestartFrequency`, new hills are temporarily written to the file:
"*output*`.colvars.`*name*`.`*replicaID*`.hills`", which serves as communication buffer. These files are only required for communication, and may be deleted after a new MD run is started with a different `outputName`.

- `replicaID` ⟨Set the identifier for this replica⟩
  Context: `metadynamics`
  Acceptable values: string
  Description: If `multipleReplicas` is `on`, this option sets a unique identifier for this replica. All replicas should use identical collective variable configurations, except for the value of this option.

- `replicasRegistry` ⟨Multiple replicas database file⟩
  Context: `metadynamics`
  Acceptable values: UNIX filename
  Default value: "*name*`.replica_files.txt`"
  Description: If `multipleReplicas` is `on`, this option sets the path to the replicas' database file.

- `replicaUpdateFrequency` ⟨How often hills are communicated between replicas⟩
  Context: `metadynamics`
  Acceptable values: positive integer
  Default value: `newHillFrequency`
  Description: If `multipleReplicas` is `on`, this option sets the number of steps after which each replica (re)reads the other replicas' files. The lowest meaningful value of this number is `newHillFrequency`. If access to the file system is significantly affecting the simulation performance, this number can be increased, at the price of reduced synchronization between replicas. Values higher than `colvarsRestartFrequency` may not improve performance significantly.

- `dumpPartialFreeEnergyFile` ⟨Periodically write the contribution to the PMF from this replica⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `on`
  Description: When `multipleReplicas` is `on`, the file *output*`.pmf` contains the combined PMF from all replicas, provided that `useGrids` is `on` (default). Enabling this option produces an additional file *output*`.partial.pmf`, which can be useful to quickly monitor the contribution of each replica to the PMF.

6.3.5 Compatibility and post-processing

The following options may be useful only for applications that go beyond the calculation of a PMF by metadynamics:

- `name` ⟨Name of this metadynamics instance⟩
  Context: `metadynamics`
  Acceptable values: string
  Default value: "`meta`" + rank number

Description: This option sets the name for this metadynamics instance. While it is not advisable to use more than one metadynamics instance within the same simulation, this allows to distinguish each instance from the others. If there is more than one metadynamics instance, the name of this bias is included in the metadynamics output file names, such as e.g. the `.pmf` file.

- `keepHills` ⟨Write each individual hill to the state file⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: When `useGrids` and this option are `on`, all hills are saved to the state file in their analytic form, alongside their grids. This makes it possible to later use exact analytic Gaussians for `rebinGrids`. To only keep track of the history of the added hills, `writeHillsTrajectory` is preferable.

- `writeHillsTrajectory` ⟨Write a log of new hills⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `on`
  Description: If this option is `on`, a logfile is written by the `metadynamics` bias, with the name "*output*`.colvars.<name>.hills.traj`", which can be useful to follow the time series of the hills. When `multipleReplicas` is `on`, its name changes to "*output*`.colvars.<name>.<replicaID>.hills.traj`". This file can be used to quickly visualize the positions of all added hills, in case `newHillFrequency` does not coincide with `colvarsRestartFrequency`.

6.4 Harmonic restraints

The harmonic biasing method may be used to enforce fixed or moving restraints, including variants of Steered and Targeted MD. Within energy minimization runs, it allows for restrained minimization, e.g. to calculate relaxed potential energy surfaces. In the context of the Colvars module, harmonic potentials are meant according to their textbook definition:

$$V(\xi) = \frac{1}{2} k \left(\frac{\xi - \xi_0}{w_\xi} \right)^2 \tag{21}$$

Note that this differs from harmonic bond and angle potentials in common force fields, where the factor of one half is typically omitted, resulting in a non-standard definition of the force constant.

The formula above includes the characteristic length scale w_ξ of the colvar ξ (keyword `width`, see 3.1) to allow the definition of a multi-dimensional restraint with a unified force constant:

$$V(\xi_1, \ldots, \xi_M) = \frac{1}{2} k \sum_{i=1}^{M} \left(\frac{\xi_i - \xi_0}{w_\xi} \right)^2 \tag{22}$$

If one-dimensional or homogeneous multi-dimensional restraints are defined, and there are no other uses for the parameter w_ξ, *the parameter* `width` *can be left at its default value of* 1.

A harmonic restraint is set up by a `harmonic` { . . . } block, which may contain (in addition to the standard option `colvars`) the following keywords:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)

- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)

- `outputEnergy`: see definition of `outputEnergy` in sec. 6 (biasing and analysis methods)

- `forceConstant` ⟨Scaled force constant (unit of energy specified by `units`)⟩
  Context: `harmonic`
  Acceptable values: positive decimal
  Default value: `1.0`
  Description: This defines a scaled force constant k for the harmonic potential (eq. 22). To ensure consistency for multidimensional restraints, it is divided internally by the square of the specific `width` for each colvar involved (which is 1 by default), so that all colvars are effectively dimensionless and of commensurate size. For instance, setting a scaled force constant of 10 kcal/mol acting on two colvars, an angle with a `width` of 5 degrees and a distance with a width of 0.5 Å, will apply actual force constants of 0.4 kcal/mol$\times$degree^{-2} for the angle and 40 kcal/mol/Å^2 for the distance.

- `centers` ⟨Initial harmonic restraint centers⟩
  Context: `harmonic`
  Acceptable values: space-separated list of colvar values
  Description: The centers (equilibrium values) of the restraint, ξ_0, are entered here. The number of values must be the number of requested colvars. Each value is a decimal number if the corresponding colvar returns a scalar, a "`(x, y, z)`" triplet if it returns a unit vector or a vector, and a "`(q0, q1, q2, q3)`" quadruplet if it returns a rotational quaternion. If a colvar has periodicities or symmetries, its closest image to the restraint center is considered when calculating the harmonic potential.

Tip: A complex set of restraints can be applied to a system, by defining several colvars, and applying one or more harmonic restraints to different groups of colvars. In some cases, dozens of colvars can be defined, but their value may not be relevant: to limit the size of the colvars trajectory file, it may be wise to disable `outputValue` for such "ancillary" variables, and leave it enabled only for "relevant" ones.

6.4.1 Moving restraints: steered molecular dynamics

The following options allow to change gradually the centers of the harmonic restraints during a simulations. When the centers are changed continuously, a steered MD in a collective variable space is carried out.

- `targetCenters` ⟨Steer the restraint centers towards these targets⟩
  Context: `harmonic`
  Acceptable values: space-separated list of colvar values
  Description: When defined, the current `centers` will be moved towards these values during the simulation. By default, the centers are moved over a total of `targetNumSteps` steps by a linear interpolation, in the spirit of Steered MD. If `targetNumStages` is set to a nonzero value, the change is performed in discrete stages, lasting `targetNumSteps` steps *each*. This second mode may be used to sample successive windows in the context of an Umbrella Sampling simulation. When continuing a simulation run, the `centers` specified in the configuration file <`colvarsConfig`> are overridden by those saved in the restart file <`colvarsInput`>. To perform Steered MD in an arbitrary space of colvars, it is sufficient to use this option and enable `outputAppliedForce` within each of the colvars involved.

- `targetNumSteps` ⟨Number of steps for steering⟩
  Context: `harmonic`
  Acceptable values: positive integer
  Description: In single-stage (continuous) transformations, defines the number of MD steps required to move the restraint centers (or force constant) towards the values specified with `targetCenters` or

`targetForceConstant`. After the target values have been reached, the centers (resp. force constant) are kept fixed. In multi-stage transformations, this sets the number of MD steps *per stage*.

- `outputCenters` ⟨Write the current centers to the trajectory file⟩
  Context: `harmonic`
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is chosen and `colvarsTrajFrequency` is not zero, the positions of the restraint centers will be written to the trajectory file during the simulation. This option allows to conveniently extract the PMF from the colvars trajectory files in a steered MD calculation.

- `outputAccumulatedWork` ⟨Write the accumulated work of the moving restraint to the trajectory file⟩
  Context: `harmonic`
  Acceptable values: boolean
  Default value: `off`
  Description: If this option is chosen, `targetCenters` is defined, and `colvarsTrajFrequency` is not zero, the accumulated work from the beginning of the simulation will be written to the trajectory file. If the simulation has been continued from a previous state file, the previously accumulated work is included in the integral. This option allows to conveniently extract the PMF from the colvars trajectory files in a steered MD calculation.

Note on restarting moving restraint simulations: Information about the current step and stage of a simulation with moving restraints is stored in the restart file (state file). Thus, such simulations can be run in several chunks, and restarted directly using the same colvars configuration file. In case of a restart, the values of parameters such as `targetCenters`, `targetNumSteps`, etc. should not be changed manually.

6.4.2 Moving restraints: umbrella sampling

The centers of the harmonic restraints can also be changed in discrete stages: in this cases a one-dimensional umbrella sampling simulation is performed. The sampling windows in simulation are calculated in sequence. The colvars trajectory file may then be used both to evaluate the correlation times between consecutive windows, and to calculate the frequency distribution of the colvar of interest in each window. Furthermore, frequency distributions on a predefined grid can be automatically obtained by using the `histogram` bias (see 6.8).

To activate an umbrella sampling simulation, the same keywords as in the previous section can be used, with the addition of the following:

- `targetNumStages` ⟨Number of stages for steering⟩
  Context: `harmonic`
  Acceptable values: non-negative integer
  Default value: `0`
  Description: If non-zero, sets the number of stages in which the restraint centers or force constant are changed to their target values. If zero, the change is continuous. Each stage lasts `targetNumSteps` MD steps. To sample both ends of the transformation, the simulation should be run for `targetNumSteps` $\times$ (`targetNumStages` + 1).

6.4.3 Changing force constant

The force constant of the harmonic restraint may also be changed to equilibrate [18].

- `targetForceConstant` ⟨Change the force constant towards this value⟩
  Context: `harmonic`
  Acceptable values: positive decimal
  Description: When defined, the current `forceConstant` will be moved towards this value during the simulation. Time evolution of the force constant is dictated by the `targetForceExponent` parameter (see below). By default, the force constant is changed smoothly over a total of `targetNumSteps` steps. This is useful to introduce or remove restraints in a progressive manner. If `targetNumStages` is set to a nonzero value, the change is performed in discrete stages, lasting `targetNumSteps` steps *each*. This second mode may be used to compute the conformational free energy change associated with the restraint, within the FEP or TI formalisms. For convenience, the code provides an estimate of the free energy derivative for use in TI. A more complete free energy calculation (particularly with regard to convergence analysis), while not handled by the Colvars module, can be performed by post-processing the colvars trajectory, if `colvarsTrajFrequency` is set to a suitably small value. It should be noted, however, that restraint free energy calculations may be handled more efficiently by an indirect route, through the determination of a PMF for the restrained coordinate.[18]

- `targetForceExponent` ⟨Exponent in the time-dependence of the force constant⟩
  Context: `harmonic`
  Acceptable values: decimal equal to or greater than 1.0
  Default value: `1.0`
  Description: Sets the exponent, α, in the function used to vary the force constant as a function of time. The force is varied according to a coupling parameter λ, raised to the power α: $k_\lambda = k_0 + \lambda^\alpha (k_1 - k_0)$, where k_0, k_λ, and k_1 are the initial, current, and final values of the force constant. The parameter λ evolves linearly from 0 to 1, either smoothly, or in `targetNumStages` equally spaced discrete stages, or according to an arbitrary schedule set with `lambdaSchedule`. When the initial value of the force constant is zero, an exponent greater than 1.0 distributes the effects of introducing the restraint more smoothly over time than a linear dependence, and ensures that there is no singularity in the derivative of the restraint free energy with respect to lambda. A value of 4 has been found to give good results in some tests.

- `targetEquilSteps` ⟨Number of steps discarded from TI estimate⟩
  Context: `harmonic`
  Acceptable values: positive integer
  Description: Defines the number of steps within each stage that are considered equilibration and discarded from the restraint free energy derivative estimate reported reported in the output.

- `lambdaSchedule` ⟨Schedule of lambda-points for changing force constant⟩
  Context: `harmonic`
  Acceptable values: list of real numbers between 0 and 1
  Description: If specified together with targetForceConstant, sets the sequence of discrete λ values that will be used for different stages.

6.5 Harmonic wall restraints

The `harmonicWalls` `{...}` bias is closely related to the harmonic bias (see 6.4), with the following two differences: *(i)* instead of a center a *lower wall* and/or an *upper wall* are defined, outside of which the bias

implements a half-harmonic potential;

$$V(\xi) = \begin{cases} \frac{1}{2}k\left(\frac{\xi-\xi_{\text{upper}}}{w_\xi}\right)^2 & \text{if } \xi > \xi_{\text{upper}} \\ 0 & \text{if } \xi_{\text{lower}} \leq \xi \geq \xi_{\text{upper}} \\ \frac{1}{2}k\left(\frac{\xi-\xi_{\text{lower}}}{w_\xi}\right)^2 & \text{if } \xi < \xi_{\text{lower}} \end{cases} \tag{23}$$

where ξ_{lower} and ξ_{upper} are the lower and upper wall thresholds, respectively; *(ii)* because an interval between two walls is defined, only scalar variables can be used (but any number of variables can be defined, and the wall bias is intrinsically multi-dimensional).

Note: this bias replaces the keywords `lowerWall`, `lowerWallConstant`, `upperWall` and `upperWallConstant` defined in the `colvar` context (see 3). These keywords are still supported, but will be deprecated in the future.

The `harmonicWalls` bias implements the following options:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)
- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)
- `outputEnergy`: see definition of `outputEnergy` in sec. 6 (biasing and analysis methods)
- `lowerWalls` ⟨Position of the lower wall⟩
  Context: `colvar`
  Acceptable values: Space-separated list of decimals
  Description: Defines the values ξ_{lower} below which a confining restraint on the colvar is applied to each colvar ξ.
- `upperWalls` ⟨Position of the lower wall⟩
  Context: `colvar`
  Acceptable values: Space-separated list of decimals
  Description: Defines the values ξ_{upper} ve which a confining restraint on the colvar is applied to each colvar ξ.
- `forceConstant`: see definition of `forceConstant` in sec. 6.4 (Harmonic restraints)
- `lowerWallConstant` ⟨Force constant for the lower wall⟩
  Context: `harmonicWalls`
  Acceptable values: positive decimal
  Default value: `forceConstant`
  Description: When both sets of walls are defined (lower and upper), this keyword allows setting different force constants for them. The force constant reported in the output as "k", and used in the change of force constant scheme, is the geometric mean of the two.
- `upperWallConstant`: analogous to `lowerWallConstant`
- `targetForceConstant`: see definition of `targetForceConstant` in sec. 6.4 (Harmonic restraints)
- `targetNumSteps`: see definition of `targetNumSteps` in sec. 6.4 (Harmonic restraints)
- `targetForceExponent`: see definition of `targetForceExponent` in sec. 6.4 (Harmonic restraints)
- `targetEquilSteps`: see definition of `targetEquilSteps` in sec. 6.4 (Harmonic restraints)

- `targetNumStages`: see definition of `targetNumStages` in sec. 6.4 (Harmonic restraints)
- `lambdaSchedule`: see definition of `lambdaSchedule` in sec. 6.4 (Harmonic restraints)

6.6 Linear restraints

The linear restraint biasing method is used to minimally bias a simulation. There is generally a unique strength of bias for each CV center, which means you must know the bias force constant specifically for the center of the CV. This force constant may be found by using experiment directed simulation described in section 6.7. Please cite Pitera and Chodera when using [19].

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)
- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)
- `forceConstant` ⟨Scaled force constant (unit of energy specified by `units`)⟩
  Context: `linear`
  Acceptable values: positive decimal
  Default value: `1.0`
  Description: This defines a scaled force constant for the linear bias. To ensure consistency for multidimensional restraints, it is divided internally by the specific `width` for each colvar involved (which is 1 by default), so that all colvars are effectively dimensionless and of commensurate size.
- `centers` ⟨Initial linear restraint centers⟩
  Context: `linear`
  Acceptable values: space-separated list of colvar values
  Description: The centers (equilibrium values) of the restraint are entered here. The number of values must be the number of requested colvars. Each value is a decimal number if the corresponding colvar returns a scalar, a "`(x, y, z)`" triplet if it returns a unit vector or a vector, and a "`q0, q1, q2, q3)`" quadruplet if it returns a rotational quaternion. If a colvar has periodicities or symmetries, its closest image to the restraint center is considered when calculating the linear potential.

6.7 Adaptive Linear Bias/Experiment Directed Simulation

Experiment directed simulation applies a linear bias with a changing force constant. Please cite White and Voth [20] when using this feature. As opposed to that reference, the force constant here is scaled by the `width` corresponding to the biased colvar. In White and Voth, each force constant is scaled by the colvars set center. The bias converges to a linear bias, after which it will be the minimal possible bias. You may also stop the simulation, take the median of the force constants (ForceConst) found in the colvars trajectory file, and then apply a linear bias with that constant. All the notes about units described in sections 6.6 and 6.4 apply here as well. **This is not a valid simulation of any particular statistical ensemble and is only an optimization algorithm until the bias has converged**.

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)
- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)
- `centers` ⟨Collective variable centers⟩
  Context: `alb`
  Acceptable values: space-separated list of colvar values
  Description: The desired center (equilibrium values) which will be sought during the adaptive linear

biasing. The number of values must be the number of requested colvars. Each value is a decimal number if the corresponding colvar returns a scalar, a "`(x, y, z)`" triplet if it returns a unit vector or a vector, and a "`q0, q1, q2, q3)`" quadruplet if it returns a rotational quaternion. If a colvar has periodicities or symmetries, its closest image to the restraint center is considered when calculating the linear potential.

- `updateFrequency` ⟨The duration of updates⟩
  Context: `alb`
  Acceptable values: An integer
  Description: This is, N, the number of simulation steps to use for each update to the bias. This determines how long the system requires to equilibrate after a change in force constant ($N/2$), how long statistics are collected for an iteration ($N/2$), and how quickly energy is added to the system (at most, $A/2N$, where A is the `forceRange`). Until the force constant has converged, the method as described is an optimization procedure and not an integration of a particular statistical ensemble. It is important that each step should be uncorrelated from the last so that iterations are independent. Therefore, N should be at least twice the autocorrelation time of the collective variable. The system should also be able to dissipate energy as fast as $N/2$, which can be done by adjusting thermostat parameters. Practically, N has been tested successfully at significantly shorter than the autocorrelation time of the collective variables being biased and still converge correctly.

- `forceRange` ⟨The expected range of the force constant in units of energy⟩
  Context: `alb`
  Acceptable values: A space-separated list of decimal numbers
  Default value: 3 k_bT
  Description: This is largest magnitude of the force constant which one expects. If this parameter is too low, the simulation will not converge. If it is too high the simulation will waste time exploring values that are too large. A value of 3 k_bT has worked well in the systems presented as a first choice. This parameter is dynamically adjusted over the course of a simulation. The benefit is that a bad guess for the forceRange can be corrected. However, this can lead to large amounts of energy being added over time to the system. To prevent this dynamic update, add `hardForceRange yes` as a parameter

- `rateMax` ⟨The maximum rate of change of force constant⟩
  Context: `alb`
  Acceptable values: A list of space-separated real numbers
  Description: This optional parameter controls how much energy is added to the system from this bias. Tuning this separately from the `updateFrequency` and `forceRange` can allow for large bias changes but with a low `rateMax` prevents large energy changes that can lead to instability in the simulation.

6.8 Multidimensional histograms

The `histogram` feature is used to record the distribution of a set of collective variables in the form of a N-dimensional histogram. It functions as a "collective variable bias", and is invoked by adding a `histogram` block to the Colvars configuration file.

As with any other biasing and analysis method, when a histogram is applied to an extended-system colvar (3.3), it accesses the value of the fictitious coordinate rather than that of the "true" colvar. A joint histogram of the "true" colvar and the fictitious coordinate may be obtained by specifying the colvar name twice in a row in the `colvars` parameter: the first instance will be understood as the "true" colvar, and the second, as the fictitious coordinate.

In addition to the common parameters `name` and `colvars` described above, a `histogram` block may define the following parameter:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)
- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)
- `outputFreq` ⟨Frequency (in timesteps) at which the histogram files are refreshed⟩
  Context: `histogram`
  Acceptable values: positive integer
  Default value: `colvarsRestartFrequency`
  Description: The histogram data are written to files at the given time interval. A value of 0 disables the creation of these files (**note:** all data to continue a simulation are still included in the state file).
- `outputFile` ⟨Write the histogram to a file⟩
  Context: `histogram`
  Acceptable values: UNIX filename
  Default value: *output*.<name>.dat
  Description: Name of the file containing histogram data (multicolumn format), which is written every `outputFreq` steps. For the special case of 2 variables, Gnuplot may be used to visualize this file.
- `outputFileDX` ⟨Write the histogram to a file⟩
  Context: `histogram`
  Acceptable values: UNIX filename
  Default value: *output*.<name>.dat
  Description: Name of the file containing histogram data (OpenDX format), which is written every `outputFreq` steps. For the special case of 3 variables, VMD may be used to visualize this file.
- `gatherVectorColvars` ⟨Treat vector variables as multiple observations of a scalar variable?⟩
  Context: `histogram`
  Acceptable values: UNIX filename
  Default value: `off`
  Description: When this is set to `on`, the components of a multi-dimensional colvar (e.g. one based on `cartesian`, `distancePairs`, or a vector of scalar numbers given by `scriptedFunction`) are treated as multiple observations of a scalar variable. This results in the histogram being accumulated multiple times for each simulation step). When multiple vector variables are included in `histogram`, these must have the same length because their components are accumulated together. For example, if ξ, λ and τ are three variables of dimensions 5, 5 and 1, respectively, for each iteration 5 triplets (ξ_i, λ_i, τ) $(i = 1, \ldots 5)$ are accumulated into a 3-dimensional histogram.
- `weights` ⟨Treat vector variables as multiple observations of a scalar variable?⟩
  Context: `histogram`
  Acceptable values: list of space-separated decimals
  Default value: all weights equal to 1
  Description: When `gatherVectorColvars` is `on`, the components of each multi-dimensional colvar are accumulated with a different weight. For example, if x and y are two distinct `cartesian` variables defined on the same group of atoms, the corresponding 2D histogram can be weighted on a per-atom basis in the definition of `histogram`.

6.8.1 Grid definition for multidimensional histograms

Like the ABF and metadynamics biases, `histogram` uses the parameters `lowerBoundary`, `upperBoundary`, and `width` to define its grid. These values can be overridden if a configuration block `histogramGrid { ... }` is provided inside the configuration of `histogram`. The options supported inside this configuration block are:

- `lowerBoundaries` ⟨Lower boundaries of the grid⟩
  Context: `histogramGrid`
  Acceptable values: list of space-separated decimals
  Description: This option defines the lower boundaries of the grid, overriding any values defined by the `lowerBoundary` keyword of each colvar. Note that when `gatherVectorColvars` is on, each vector variable is automatically treated as a scalar, and a single value should be provided for it.

- `upperBoundaries`: analogous to `lowerBoundaries`

- `widths`: analogous to `lowerBoundaries`

6.9 Probability distribution-restraints

The `histogramRestraint` bias implements a continuous potential of many variables (or of a single high-dimensional variable) aimed at reproducing a one-dimensional statistical distribution that is provided by the user. The M variables $(\xi_1, \ldots, \xi_M)$ are interpreted as multiple observations of a random variable ξ with unknown probability distribution. The potential is minimized when the histogram $h(\xi)$, estimated as a sum of Gaussian functions centered at $(\xi_1, \ldots, \xi_M)$, is equal to the reference histogram $h_0(\xi)$:

$$V(\xi_1, \ldots, \xi_M) = \frac{1}{2} k \int \left(h(\xi) - h_0(\xi)\right)^2 \mathrm{d}\xi \tag{24}$$

$$h(\xi) = \frac{1}{M\sqrt{2\pi\sigma^2}} \sum_{i=1}^{M} \exp\left(-\frac{(\xi - \xi_i)^2}{2\sigma^2}\right) \tag{25}$$

When used in combination with a `distancePairs` multi-dimensional variable, this bias implements the refinement algorithm against ESR/DEER experiments published by Shen *et al* [21].

This bias behaves similarly to the `histogram` bias with the `gatherVectorColvars` option, with the important difference that *all* variables are gathered, resulting in a one-dimensional histogram. Future versions will include support for multi-dimensional histograms.

The list of options is as follows:

- `name`: see definition of `name` in sec. 6 (biasing and analysis methods)

- `colvars`: see definition of `colvars` in sec. 6 (biasing and analysis methods)

- `outputEnergy`: see definition of `outputEnergy` in sec. 6 (biasing and analysis methods)

- `lowerBoundary` ⟨Lower boundary of the colvar grid⟩
  Context: `histogramRestraint`
  Acceptable values: decimal
  Description: Defines the lowest end of the interval where the reference distribution $h_0(\xi)$ is defined. Exactly one value must be provided, because only one-dimensional histograms are supported by the current version.

- `upperBoundary`: analogous to `lowerBoundary`

- `width` ⟨Width of the colvar grid⟩
  Context: `histogramRestraint`
  Acceptable values: positive decimal
  Description: Defines the spacing of the grid where the reference distribution $h_0(\xi)$ is defined.

- `gaussianSigma` ⟨Standard deviation of the approximating Gaussian⟩
  Context: `histogramRestraint`
  Acceptable values: positive decimal
  Default value: $2 \times$ `width`
  Description: Defines the parameter σ in eq. 25.

- `forceConstant` ⟨Force constant (unit of energy specified by `units`)⟩
  Context: `histogramRestraint`
  Acceptable values: positive decimal
  Default value: `1.0`
  Description: Defines the parameter k in eq. 24.

- `refHistogram` ⟨Reference histogram $h_0(\xi)$⟩
  Context: `histogramRestraint`
  Acceptable values: space-separated list of M positive decimals
  Description: Provides the values of $h_0(\xi)$ consecutively. The mid-point convention is used, i.e. the first point that should be included is for ξ = `lowerBoundary+width/2`. If the integral of $h_0(\xi)$ is not normalized to 1, $h_0(\xi)$ is rescaled automatically before use.

- `refHistogramFile` ⟨Reference histogram $h_0(\xi)$⟩
  Context: `histogramRestraint`
  Acceptable values: UNIX file name
  Description: Provides the values of $h_0(\xi)$ as contents of the corresponding file (mutually exclusive with `refHistogram`). The format is that of a text file, with each line containing the space-separated values of ξ and $h_0(\xi)$. The same numerical conventions as `refHistogram` are used.

- `writeHistogram` ⟨Periodically write the instantaneous histogram $h(\xi)$⟩
  Context: `metadynamics`
  Acceptable values: boolean
  Default value: `off`
  Description: If `on`, the histogram $h(\xi)$ is written every `colvarsRestartFrequency` steps to a file with the name *output*`.<name>.hist.dat` This is useful to diagnose the convergence of $h(\xi)$ against $h_0(\xi)$.

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